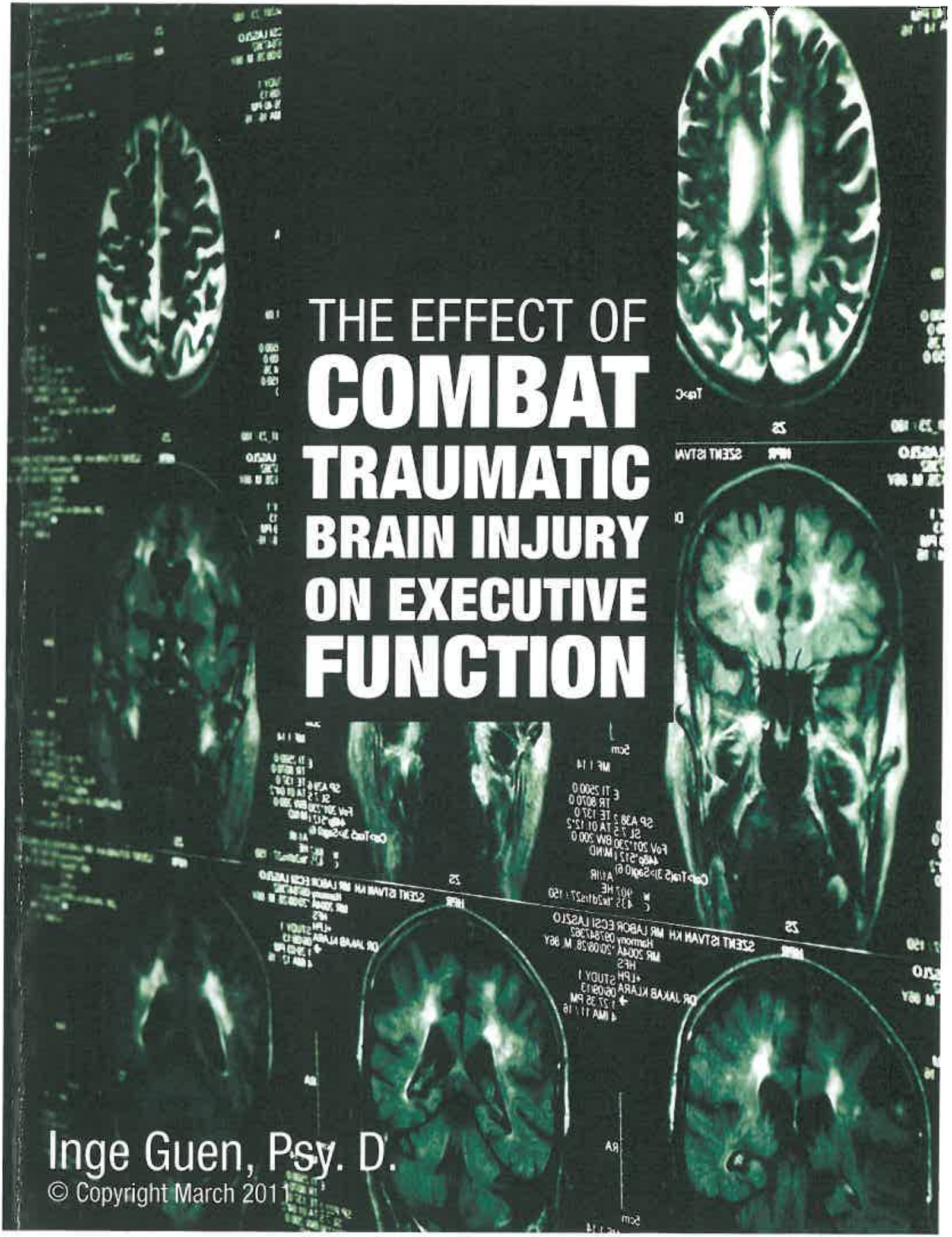

THE EFFECT OF COMBAT TRAUMATIC BRAIN INJURY ON EXECUTIVE FUNCTION

Inge Guen, Psy. D.

Report Documentation Page

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
MAR 2011		**00-00-2011 to 00-00-2011**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
The Effect of Combat Traumatic Brain Injury on Executive Function	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **National Naval Medical Center,8901 Rockville Pike,Bethesda,MD,20889**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT **unclassified**	b. ABSTRACT **unclassified**	c. THIS PAGE **unclassified**	**Same as Report (SAR)**	**123**	

THE EFFECT OF

COMBAT

TRAUMATIC BRAIN INJURY

ON

EXECUTIVE FUNCTION

Inge Guen, Psy.D.

Acknowledgements

This publication is a copy of a doctoral project submitted in partial fulfillment of the requirements for the Doctor of Psychology degree of California Southern University, Irvine, California. I am very appreciative of the support of CAPT Ronald Smith, MD, PhD, USN (Retired), former Chief of Psychiatry at the National Naval Medical Center (NNMC), Bethesda, Maryland, who was my clinical supervisor; David Williamson, MD, Director, Inpatient Traumatic Brain Injury Unit at the NNMC, who suggested this topic for my doctoral project; Anne Holman, MLS, System Librarian at the NNMC, who acquired many of the papers I reviewed; and Benton Allen, PhD, of California Southern University, who provided encouragement and guidance as my doctoral project chair. It is dedicated to the thousands of wounded warriors from the wars in Iraq and Afghanistan who have given so much for their country and face a long and difficult future, and especially the patients I am honored to work with at the National Naval Medical Center.

TABLE OF CONTENTS

CHAPTER 1: INTRODUCTION 1

Historical Context 1
Background of the Problem 3
Purpose of this Study 4
Theoretical Framework 5
Research Questions 7
Importance of the Study 7
Definition of Terms 9
Research Methods 10

CHAPTER 2: LITERATURE REVIEW 12

A. Organic Issues 12
Traumatic Brain Injury 12
TBI in the General Population 15
TBI in the Military 17
Blast TBI 24
Pathobiology of TBI 28

B. Cognitive Issues 30
Cognition 30
Relevant Components of Human Cognition 31
The Central Executive 35
Assessment of Executive Function 38
Neurological and Biological Studies of Executive Function 51

C. Clinical Issues 61
Clinical Presentation of Executive Dysfunction 61
Comorbidity 64
Therapy & Rehabilitation 59
Challenges to Cognitive Rehabilitation Therapy 78

CHAPTER 3: SUMMARY & CONCLUSIONS 82

Methodology & Analysis 82
Summary of Findings 83
Conclusions & Clinical Implications 95
Future Research 98
Concluding Comments 100

REFERENCES 103

CHAPTER 1: INTRODUCTION

Historical Context

On September 11, 2001, the world changed in ways not fully appreciated at the time. Dozens of terrorist attacks and bombings on civilian targets had been experienced in many countries in the second half of the 20th Century, including several in Europe (Provisional Irish Republican Army (IRA) in the United Kingdom; the Red Army Faction (RAF) in Germany; the Basque Homeland and Freedom (ETA) in Spain; and the Algerian Islamist Movement (MIA) in France). Some non-European countries had been targets for ongoing terrorism for decades due to fundamental religious differences, especially Israel. And even the United States had experienced two major domestic terrorist attacks in the 1990s; the World Trade Center (1993) bombing that killed 6 and injured at least 1,040 others, and the Oklahoma City bombing (1995) that killed 168 and injured 680 others.

However, there had never been an attack planned and carried out by terrorists trained in another country against civilians in the U.S. that resulted in such an enormous loss of life (2,992 dead or missing) in one coordinated series of events. What also made this attack unique was the scope of the damage done in less than one hour by only 19 terrorists, based on careful and creative planning and a commitment to a religious belief in their cause. 'Nine-eleven' became the worldwide expression for a new form of international terrorism that set the stage for a massive investment of U.S. resources in a conflict unlike anything seen before.

Independent of any political judgment about decisions made in response to this attack, the US armed forces were called upon to deploy hundreds of thousands of troops

for a combat operation that is now in its tenth year. Unlike the drafted military services used for the Vietnam War that left 58,000 service members dead and 350,000 wounded, or the 1991 Gulf War, where a coalition force from 34 collaborating countries drove Iraq out of Kuwait in less than 100 hours after the ground campaign started with only 148 US combat deaths and 467 injuries, the military services called upon for this new conflict operate with active duty, national guard, and reserve units to fight loosely organized but ideologically committed nationals in two countries, Iraq and Afghanistan. These two combat operations, Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF), have cost more than one trillion dollars, and have resulted in the combat deaths of 4,617 young men and women and left 42,020 more wounded in action and suffering from identified injuries that have changed their lives for ever (U.S. Department of Defense, 2011).

The so-called 'signature wound' of OIF and OEF is traumatic brain injury (TBI). It is interesting historically to realize that this has come full circle since World War I, when 'shell shock' was the 'signature wound' of that conflict also. It is now thought that mild TBI from the current wars is no more a 'signature' injury than it was in WWI, and that disorders that cross physical and psychological boundaries need careful interpretation and treatment (Jones, E., et al, 2007). Combat TBI can exist without any physical appearance of trauma or comorbid with severe body injuries, including multiple limb amputations and massive penetrating head wounds. This study focuses on changes in executive function due to combat TBI and what can be done to address the resulting mental suffering so that these warriors can return to their units or re-enter civilian life and function as normally as possible for the many years that lie ahead of them.

Background of the Problem

TBI is typically classified as mild, moderate, or severe depending on the level of loss of consciousness (LOC) and posttraumatic amnesia (PTA). A fourth level is also used in the military classification to account for penetrating TBI. For the period 2000 to September 30, 2010, 195,547 cases of TBI had been accounted for due to these two conflicts. However the data do not identify what percentage is due solely to direct combat operations. Of these, 77% were classified as mild, 17% moderate, 1% severe, and 2% penetrating, with the rest not classifiable (U.S. Department of Defense, 2010).

TBI is not a psychological condition; it is a physical trauma of brain tissue that can result in changes in cognition and behavior. When compounded with actual psychopathology comorbid with combat TBI, such as depression and posttraumatic stress disorder (PTSD), the mental status of these young warriors needs a full evaluation of all cognitive domains, especially executive functioning as this is critical for compliance and participation in psychotherapy to treat the depression and PTSD.

Using the latest clinical and research techniques the impact of TBI on brain structure and activity has been studied comprehensively. Medical researchers are now able to quantify changes in the microanatomy and the electrical activity of the brain, and locate areas of damage, in those with TBI. All of this is intellectually interesting but does not address the ultimate concern of how a patient whose cognitive skills have been adversely affected can 'function in the real world'. The issue of executive function is one of the key aspects of determining and following the progress of patients, as without a certain level of executive function patients are not able to take care of themselves adequately for normal daily living tasks. While a change of, say, cognitive 'processing

speed' can lead to slower responses in patients due to TBI, being slower at a task does not necessarily make that person unable to function in today's society. But if the patient's ability to organize, plan, compare options, and make decisions is compromised, life can become a series of confused situations and, sometimes, lead to unsuitable reactions to external stimuli.

Perhaps one of the most famous examples of 'combat related' TBI was Henry VIII. He had excellent health as a young man, and was recognized for his 6ft 1in and 32 in waist physique. When he was jousting (two armored horsemen charging at each other with wooden lances) at the age of 32 he failed to lower his visor and was hit by his opponent's lance just above the right eye, with no report of serious injury other than migraine headaches. However, 12 years later, in 1536, and 44 years old, he was thrown from his horse which then, also heavily armored, fell on top of him. He was unconscious for 2 hours and was considered fatally injured. Even though he eventually recovered, he was never the same person again. He went from being a sporty, promising, generous young king, to a cruel, paranoid and vicious tyrant, and the turnover in wives accelerated. He died in 1547 at the age of 56 weighing almost 400 pounds (McCarthy, M., 2009).

Purpose of this Study

The purpose of this study is to bring together in one document the most relevant basic and clinical research on how combat TBI affects executive functioning of soldiers returning from Iraq and Afghanistan, and to identify the most ecologically valid approaches for assessing and treating executive functioning changes caused by combat TBI.

The question of the effects of combat TBI on executive function is important as thousands of young warriors with mild TBI and no outward sign of trauma will face difficulties as they likely have long lives ahead of them. While some have multiple wounds (including amputations or severe head trauma) the vast majority is physically fit and has no apparent injuries. Unless the potential impact of blast TBI on executive function is understood and how to identify it quickly and treat it effectively, these young men and women can face problems making sound decisions that could affect their quality of life and financial potential. This also could become a major public health issue and have significant healthcare economic implications.

Theoretical Framework

The study of cognition, "an area within psychology that describes how we acquire, store, transform and use knowledge" (Matlin, M.W., 2009, p. 2), was a subject of philosophy well before psychology was established as a scientific discipline in late 19th Century, by Wilhelm Wundt (1832-1920) in Leipzig, Germany. A key part of this area of study is memory. Unless information is encoded in memory and recalled appropriately we are only operating as a system of reflex arcs like lower forms of life. What sets humans, and to some extent all primates, apart from other species is the ability to 'think' and 'plan' and 'organize', i.e., to operate independently and express individual thoughts and behaviors.

Following the original research of Hermann Ebbinghaus (1850-1909) in which he memorized combinations of nonsense syllables and measured how long he could retain them, George Miller (1956) "suggested that people can remember about seven items

(give or take two), that is, between five and nine items" at a time (Matlin, M.W., 2009, p. 96). At that time memory was considered to be made up of two parts; short-term memory (STM), which held information for a relatively short period (up to 30 seconds), and long-term memory (LTM), a more permanent storage system that was based on the initial evaluation of information from STM. "The most influential two-component model was that of Atkinson and Shiffrin (1968), who proposed that information came in from the environment into a temporary short-term storage system which served as an antechamber to the more durable LTM. In their model, the temporary system also served as a working memory, a workspace necessary not only for long-term learning, but also for many other complex activities such as reasoning and comprehension" (Baddeley, A., 2003, p. 190).

In 1974 Baddeley and Hitch expanded the memory model to take into account certain research findings regarding a string of random numbers that had to be rehearsed in order, while at the same time performing a spatial reasoning task. "Specifically, this study suggested that people can indeed perform two tasks simultaneously - for instance, one task that requires verbal rehearsal and another task that requires visual or spatial judgments" (Matlin, M. W., 2009, p. 106).

This led Baddeley and his colleagues to propose a new structure for STM, which they called working memory (WM), composed of a visuospatial sketchpad to hold visual information, a phonological loop to hold auditory information, and a central executive that, while not storing any information, would operate the system efficiently and allow both enhancement and suppression of information so that the mind could stay on target and focus on tasks, and not be distracted by all the other incoming extraneous

information from sensory input and feedback from long-term memory. In 2000 they added another component, an episodic buffer, to account for newer research findings, which "serves as a temporary storehouse where we can gather and combine information form the phonological loop, the visuospatial sketchpad, and long term memory" (Matlin, M. W., 2009, p. 113).

However, it is the central executive that seems to be the critical element in the model as "it almost certainly is the most important component in terms of its general impact on cognition" (Baddeley, A., 1996, p. 5). Thus the impact of combat TBI on the central executive and how this affects executive functioning is the basis of this study.

Research Questions

The fundamental questions that will be raised in this project are: 1) does combat TBI affect executive functioning and, if so, 2) are these changes amenable to treatment so that executive functioning of combat TBI patients can be improved for daily living requirements and also help to make the treatment of comorbid conditions more effective?

Importance of the Study

Of all cognitive domains, the one that helps us operate most efficiently and not simply respond to the latest stimulus is executive function. Without this central executive system (CES) as originally proposed by Baddeley and colleagues, that allows us to plan and chose, organize and schedule, our lives would be a series of responses to the most current visual or auditory stimuli. We would have difficulty deciding what is more important to do now rather than later, and our behavior would become almost childlike. Executive function takes years to develop fully and affects many different facets of

children's mental development, from their understanding of other people's points of view to their ability to focus on a task. If executive function goes awry, it may result in disorders such as autism and attention-deficit/hyperactivity disorder (Zelazo, P.D., 2005). As children grow they learn to chose and select, and this process continues to develop through adolescence and into young adulthood. But even at this stage of development executive function is still evolving, as evidenced by certain adolescent behaviors that are dangerous, such as drunk driving and risky sexual activity, and the insurance industry response by placing them at high risk. This is the corporate demonstration that executive function has not reached the level of maturity that it will in later life. In old age executive function diminishes and creates different problems for making decisions or choosing wisely.

In general cognitive changes are not that well documented in combat TBI patients, and specifically executive functioning even less so. The pathological/structural issues are studied, and medical and surgical treatments of the physical damage are well documented. The fact that so many warriors with severe head trauma are alive is a testament to the skills of military doctors in theater and at the tertiary medical centers to which they are evacuated within days of the battlefield trauma, such as the National Naval Medical Center, Bethesda, Maryland, and the Walter Reed Army Medical Center, Washington, DC. But when the surgery is over and the life has been saved, what is then even more important is how that soldier can regain the ability to be an effective warrior and/or to become a productive member of civilian society. With poor executive function some of the basics of cognitive performance are missing making it impossible to perform normal acts of daily living and to work productively. As this has major public health and

socio-economic implications, identifying the most efficacious therapeutic approaches that will help the clinician to focus on this special facet of cognition can be a foundation for the other therapies that may be necessary to bring the soldier back to maximum obtainable mental capacity. For example, without an acceptable level of executive functioning, using cognitive behavioral therapy (CBT) to treat PTSD could be ineffective. Executive functioning is needed for success with all psychotherapeutic processes; therefore understanding how this may be affected by combat TBI can improve outcomes and save time.

Definition of Terms

- Central executive system (of working memory): integrates information from the phonological loop, the visuospatial sketchpad, the episodic buffer, and long-term memory
- Cognition: an area within psychology that describes how we acquire, store, transform and use knowledge.
- Combat: direct and live engagement with an enemy whose intent is to kill or maim the subject
- Depression: a clinical psychological condition characterized by sadness, hopelessness, fatigue, and lack of interest in leisure activities.
- Executive function: the conscious control of what we think and do; the ability to plan and organize our daily lives and work

- Improvised explosive device (IED): a homemade bomb constructed and deployed in a manner inconsistent with conventional military action, including the explosive formed penetrator (EFP).
- Neuropsychological tests: standardized tests presented to subjects to assess cognitive skills in a manner that allows comparison to population norms
- Traumatic brain injury (TBI): damage to the brain after trauma (e.g., a blow or jolt to the head, a penetrating head injury, or exposure to an external energy source)
- Posttraumatic stress disorder (PTSD): characteristic symptoms following exposure to an extreme stressor that involves actual or threatened death or injury.
- Psychopathology: clinically significant abnormal and maladaptive behavior, also known as abnormal psychology
- Warrior: a military combat team member, i.e., a soldier or marine, who actually engages in live combat operations, not in a support role.

Research Methods

Articles published in peer-reviewed journals selected from both Internet searches using key words such as 'executive function', traumatic brain injury', and 'TBI', and library research at the National Naval Medical Center, Bethesda, Maryland, will be reviewed against the study questions. The basic biophysical aspects of combat TBI, the resulting blast induced neurotrauma (BINT) and penetrating wounds, and the cognitive and behavioral effects of combat TBI will be studied. Thus this will be an extensive literature review to determine what is known about TBI from civilian studies compared

with the latest information from combat TBI, focusing on a critical component of cognition - executive function; how to measure it, how to determine changes that occur, and how to rehabilitate it when necessary.

CHAPTER 2: LITERATURE REVIEW

In order to eventually reach the point of exploring the effect of traumatic brain injury (TBI) as a result of combat activities on executive function it is necessary to gain a clear understanding of each of these two phenomena: TBI, as a biological and pathophysiological entity (i.e., organic issues); and executive function, as an important element of cognition and its role in human behavior (i.e., cognitive issues).

A. ORGANIC ISSUES

Traumatic Brain Injury

A term that is used incorrectly as synonymous with TBI in some scientific journals and by the mainstream press is acquired brain injury (ABI), to reflect a brain injury resulting from some external source. However, an ABI can be due to events unrelated to any traumatic situation, such as toxins crossing the blood-brain barrier and a stroke. Thus ABI is a much broader term for damage to the brain after birth, of which TBI is a specific example. While there can be an acquired injury from a number of sources, a TBI is defined by the fact that the cause of the injury is an incident involving trauma to the head, hence the word 'traumatic'. This also leads some to use the term traumatic head injury, but that limits the outcome to damage to the external structures of the head and does not refer to an internal brain injury. This paper uses TBI explicitly to refer to brain injury due to a physical traumatic event, not due to some medical condition that can affect brain tissue and also lead to cognitive deficits, or simply head injuries

alone. Also, it is important to emphasize that TBI is not a mental health condition; it is a physical injury of the brain.

There are a number of medical definitions of TBI that are specific to the source and healthcare specialty. One that is clear, comprehensive, and applicable to most TBI situations is "a nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness" (Dawodu, S., 2009, p. 1). A more focused definition published in what has become the 'encyclopedia' for health professionals working in military medicine and attending to the injuries of warriors from the wars of Afghanistan and Iraq is "damage to the brain after trauma (for example, a blow or jolt to the head, a penetrating head injury, or exposure to an external energy source)" (IOM, 2009, p. 14).

The US Department of Defense (DoD) definition of TBI adopted on October 1, 2007, for use with wounded service personnel is:

"A traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event:

- Any period of loss of or a decreased level of consciousness;
- Any loss of memory for events immediately before or after the injury;
- Any alternation in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.);
- Neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient;

- Intracranial lesion.

External forces may include any of the following events: the head being struck by an object, the head striking an object, the brain undergoing an acceleration/deceleration movement without direct external trauma to the head, a foreign body penetrating the brain, forces generated from events such as a blast or explosion, or other force yet to be defined" (Casscells, S.W., 2007).

TBI is also assigned different forms, i.e., open (with a penetrating wound) or closed, and severity levels, i.e., mild, moderate, or severe. The common term 'concussion' is synonymous with mild (mTBI or MTBI). TBI severity is categorized most often with the Glasgow Coma Scale (GCS) based on a clinical assessment within 48 hours of injury. More recently, with greater attention to immediate care for patients with potential TBI, this time frame has been reduced to 6 hours where possible, i.e., to be as soon after the incident as medically feasible given all the other medical procedures that are usually required by a trauma patient. The GCS has three domains of scoring; eye opening (1-4), verbal response (1-5), and motor function (1-6), with a possible combined score range of 3 (comatose or nonresponsive) to 15 (no deficits in any of the three domains) (U.S. Department of Health and Human Services, 2003). Other clinical measures of single outcomes are the duration of loss of consciousness (LOC) and posttraumatic amnesia (PTA). Modern imaging techniques are also used to assess severity, and will be discussed below with reference to research on brain structure changes due to TBI.

TBI in the General Population

Each year in the United States approximately 1.7 million people sustain a TBI. Of these 52,000 (3%) die, 275,000 (16%) are hospitalized, and 1,365,000 (81%) are treated and released from an emergency department. Approximately 511,000 TBIs occur among children ages 0 to 14 years and emergency department visits account for more than 90% of the TBIs in this age group. Falls are the leading cause of TBI, with rates highest for children ages 0 to 4 years and for adults 75 years or older. In every age group, TBI rates are higher for males than for females. Falls result in the greatest number of TBI-related hospitalizations. Adults ages 75 years or older have the highest rates of TBI-related hospitalization and death. Motor vehicle-traffic (MVT) injury is the leading cause of TBI-related death, with rates being highest for ages 20 to 24 years (Faul M., et al, 2010). In addition, an estimated 124,626 people with TBI experience long-term impairment or disability from their injury each year (Selassie, A.W., et al, 2008).

These data are from emergency department visits, hospitalizations, and deaths for the years 2002 through 2006. However, even with these clean data "an estimated 439,000 TBIs treated by physicians during office visits and 89,000 treated in outpatient settings were not included in this report. In addition, TBIs with no medical advice sought, an estimated 25% of all mild and moderate TBIs, were not included." Further "this report does not include TBIs from federal, military, or Veterans Administration (VA) hospitals" (Faul M., et al, 2010, p. 61).

While this information on the incidence (annual occurrence) of TBI in the civilian population is useful, the prevalence (cumulative occurrence from all years) of TBI is not as readily available. However, based on data from published reports on state models,

"the CDC estimated that 5.3 million US citizens (2%) were living with TBI-related disability in 1996. If that proportion is applied to the 2007 US population of over 301 million people, then just over 6 million people are living with the effects of TBI, and 2 million people have unmet health service needs" (IOM, 2009, p. 63). One major risk factor for TBI in adults is alcohol consumption, where intoxication can greatly increase risks for motor-vehicle accidents, self-inflicted injury, falls, and assault. A number of studies have documented the association between blood alcohol concentration (BAC) and the risk of TBI, including data that show that over 40% of TBIs from driving accidents had BACs of 0.10% or higher (IOM, 2009, p.65).

Significant interest in head-to-head tackles and other injuries in American football has resulted in a few research studies based on data from retired players of the National Football League (NFL) to assess the long-term effects of mTBI (concussion). While the literature is not extensive, and the methods tend to rely on self-reports using questionnaires, one study found that 61% of 2,552 retired professional football players with an average playing career of 6.6 years had suffered at least one concussion during this period, and 24% had sustained three or more concussions. Follow-up questionnaires to 758 of these retired players over 50 years of age examined the prevalence of mild cognitive impairment (MCI) and found that there was an association between recurrent concussion and MCI. "Retired players with three or more reported concussions had a fivefold prevalence of MCI diagnosis and a threefold prevalence of reported significant memory problems compared with retirees without a history of concussion." While no direct association between recurrent concussion and Alzheimer's disease was found, the authors did find an earlier onset of Alzheimer's disease in the retired football payers with

recurrent concussion than in the general American male population (Guskiewicz, K.M., et al, 2005, p.719). In another study of the same population, an association was found between recurrent concussion and the diagnosis of lifetime depression (Guskiewicz, K.M., et al, 2007).

Boxing is another contact sport that attracts interest due to the ultimate goal of a knockout or 'KO' (i.e., loss of consciousness). A search of the literature to find information about the incidence and prevalence of mTBI (concussion) in professional boxing was quite unsuccessful. Despite the popularity of the image of the 'punch drunk' boxer and the associated exotic medical term 'dementia pugilistica', more properly chronic traumatic encephalopathy (CTE), few articles address this issue with solid data. "What is known is that boxing mortality rates are comparable to other high-risk sports, and long-term neurologic compromise in boxers is found in only a small percentage of those involved in the sport, more often in professional fighters with extensive careers" (Heilbronner, R.L., et al, 2009, p. 17). The literature on amateur boxing is also sparse, yet the studies that have been published tend to be of higher quality. And they all conclude there is no strong evidence to associate chronic traumatic brain injury with amateur boxing (Loosemore, M., et al, 2007; Porter, M.D., 2003). Given the requirements for headgear, fewer rounds, and the stronger attention to point scoring rather than knockouts, this conclusion is logical.

TBI in the Military

While the data for civilian incidence and prevalence of TBI are incomplete due to non-reporting or not seeking medical care after falls, motor vehicle accidents, or assaults,

plus lack of data from federal hospitals, the same problems regarding accurately compiling data exist within the US military. Data collected by the Military Health System (MHS) from electronic medical records is analyzed by the Defense and Veterans Brain Injury Center (DVBIC), which since 2007 is the single office of responsibility for consolidation of all TBI-related incidence and prevalence information for the Department of Defense (DoD), in cooperation with the Armed Forces Health Surveillance Center (AFHSC). Data on TBI in the military that have been compiled since 2000 and are updated quarterly, are based solely on medical records with a clinical diagnosis. Thus these data are often less than reported in the literature due to the use of other assessment methods, such as self-reporting using medical questionnaires or other data sets that are not based on clinical diagnoses by health professionals. Unfortunately, even though these data are based on actual medical diagnoses of TBI within the U.S. Military, the MHS is unable to provide information regarding cause of injury or location because that information is not available in most medical records.

From 2000 through the third quarter of 2010 (essentially the decade of the wars in Iraq and Afghanistan) a total of 195,547 clinical diagnoses of TBI had been made in the US Military (all branches). Of this total 3,367 (1.7%) were penetrating, or open head, injury; 2,038 (1.0%) were severe (closed head injury); 33,020 (16.9%) were moderate; 150,222 (76.8%) were mild; and 6,900 (3.5%) were not classifiable (U.S. Department of Defense, 2010). The severity of injury was ascertained by using ICD-9 codes used in the clinical records, and the following levels of TBI, from least to greatest:

"Concussion/Mild TBI: A confused or disoriented state which lasts less than 24 hours; loss of consciousness for up to 30 minutes; memory loss lasting less than 24 hours; and structural brain imaging (MRI or CT scan) yielding normal results.

Moderate TBI: A confused or disoriented state which lasts more than 24 hours; loss of consciousness for more than 30 minutes but less than 24 hours; memory loss lasting greater than 24 hours but less than seven days; and structural brain imaging yielding normal or abnormal results.

Severe TBI: A confused or disoriented state which lasts more than 24 hours; loss of consciousness for more than 24 hours; memory loss for more than seven days; and structural brain imaging yielding normal or abnormal results.

Penetrating TBI, or open head injury, is a head injury in which the dura mater, the outer layer of the meninges, is penetrated. Penetrating injuries can be caused by high-velocity projectiles or objects of lower velocity, such as knives or bone fragments from a skull fracture that are driven into the brain" (U.S. Department of Defense, 2010).

These data are for all branches of the military and for all personnel, and include traumatic incidents similar to those occurring in the civilian data, such as motor vehicle accidents or falls during training, in addition to those associated with combat in Iraq and Afghanistan or other active duty operations around the world. Unfortunately, while these records are complete and based on clinical diagnoses, the cause and location of the injury are not routinely reported. For example, the Army (Active, Guard and Reserves) incidence of TBI in 2000 was 4,613 of a total of 10,963 for all branches, i.e., 42%, whereas in 2009 (the most recent full year of data) the Army incidence was 19,028 of a total of 29,223, i.e., 65%. The comparable incidence data for Marines (Active and

Reserves) was 1,782, i.e., 16%, and 3,861, i.e., 13%. The fact that the Marines percentage stayed essentially the same even though the numbers doubled suggests different battlefield operations than those of the Army. The significant increase is the Army is certainly due to the wars in Iraq and Afghanistan as this branch of the military was carrying the bulk of the ground combat operations, especially those facing blasts from improvised explosive devices (IEDs) (U.S. Department of Defense, 2010).

Despite all the capabilities within the DoD for tracking battlefield incidence, there are no official reports on the numbers of TBI cases resulting from actual combat experience in theatre. Consequently, it is necessary to rely on other population-based studies for the actual incidence and causes of combat TBI. A number of articles have been published in peer-reviewed journals or in monographs published by defense contractors.

One often-cited study reported on a brigade combat team (BCT) returning from a 1-year deployment to Iraq had clinician-confirmed (as opposed to self-reported) mTBI. This study estimated that 65% of the soldiers deployed to Iraq had seen combat, and 88% of the injuries were the result of blasts. The unit of 3,973 soldiers was screened post-deployment using the Warrior Administered Retrospective Casualty Assessment Tool (WARCT), which facilitated follow-up clinical interviews. Based on the injury history and associated somatic and neuropsychological symptoms, mild TBI was identified in 22.8% of the population evaluated (Terrio, H., et al, 2009).

Another general story that is cited in a number of other articles, based on interviews with researchers, clinicians and patients, reported that 22% of wounded soldiers going through Landstuhl Regional Medical Center, Germany, had injuries to

head, face or neck, according to the Joint Theatre Trauma Registry, compiled by the U.S. Army Institute of Surgical Research (Okie, S., 2005). "Injuries to the brain have often been categorized as 'head and neck' injuries. Thus, it may be difficult to know the precise number of TBIs that occur, and comparisons to prior wars are influenced by possible changes in data-gathering methodologies" and "in previous conflicts such as Operation Desert Storm, about 20% of those treated for wounds had head injuries" Warden, D., 2006, p. 398).

Another often-cited study was based on a survey of 2,525 Army infantry soldiers 3 to 4 months after returning from a yearlong deployment to Iraq. Of this group 4.9% reported injuries with LOC and 10.3% with 'altered mental status', i.e., in combination indicating an incidence of mTBI of 15% in post-deployment soldiers (Hoge, C.W., et al, 2008). Another telephone study of 1,965 previously deployed individuals sampled from 24 geographic areas found 19% reported a probable TBI during deployment. This study concluded that of the 1.64 million deployed for OIF and OEF as of Oct 2007, 320,000 suffer from TBI, 57% of which had not been evaluated by a physician for brain injury (Tanielan, T. & Jacox, L.H. (eds), 2008).

However, Hoge and colleagues also point out that potential flaws in these reports stem from the clinical definition of 'concussion/mild TBI' adopted by the Departments of Defense and Veterans Affairs. They claim that trying to diagnose TBI at the time of the battle, when other aspects of the war are still fresh, is not appropriate as "an alteration of consciousness in combat may also result from normal responses to injury, acute stress, dissociation, sleep deprivation, syncope, or the confusion of war" (Hoge, C.W., et al, 2009, p. 1589). In fact they suggest that mTBI might be over diagnosed in some studies,

which then leads to unclear treatment strategies as the mTBI could be (and often is) comorbid with psychopathology like PTSD and depression.

But taken as a whole, while the precise number of TBI patients from combat operations is not well quantified, it seems clear from the literature that 15-23% of soldiers who had seen combat in Iraq and who were not evacuated out of theater due to severe injuries, were suffering from mTBI at least one year after deployment. "Of all the individuals medically evacuated to the WRAMC [Walter Reed Army Medical Center] who sustained injuries from hostile forces, 28% had TBI. Mild TBI accounted for less than half of the sample, whereas moderate and severe (including penetrating) accounted for 56%. Penetrating brain injury was seen in 12% of the total group; closed TBI accounted for 88% of the group, confirming that closed brain injury in more common in this war" (Warden, D., 2006, p. 400).

So essentially, there are two distinct populations of warriors suffering from TBI. First, those who made it home as functioning soldiers with no apparent injury, yet with the likelihood that approximately 20% were suffering from mTBI (and post concussive symptoms) of which at least 50% did not receive any medical care. Second, those who were evacuated out of theater and hospitalized due to significant injury, of which approximately 28% were identified with TBI; 60% with moderate or severe TBI as a result of their injuries (including 12% due to penetrating head wounds), and another 40% suffering from mTBI. And while there is great concern and compassion for the warriors who lost limbs in the current wars, the number of serious brain injuries is approximately 5 times the number of amputees (Warden, D., 2006).

To put this in a broad structural perspective, a literature review of 286 papers called for a more complete model of TBI as a medical condition resulting from combat operations. The authors identify five neuropsychological symptoms that can be grouped into a systematic classification of combat TBI: "1) *cognitive dysfunctions* (difficulties in memory, attention, language, visuospatial cognition, sensory-motor integration, affect recognition, and/or executive function) due to neocortical damage; 2) *neurobehavioral disorders* (mood, affect, anxiety, posttraumatic stress, etc.) due to damage to the cortex, limbic system, and/or brain stem; 3) *sensory disruptions* (impaired smell, vision, hearing equilibrium, taste, and somatosensory perception) due to trauma to sensory organs or their projections; 4) *somatic symptoms* (headache and chronic pain); 5) *substance dependence*" (Halbauer, J.D., et al, 2009, p. 757). They point out that with such an array of possible sequelae from combat TBI, some will be overlooked unless a multidimensional approach (e.g., a biopsychosocial model) is applied to each of the five symptom clusters. This model is comprehensive and provides a useful structure to approach war-related TBI.

From a clinician's viewpoint, the exact numbers of TBI patients, both civilian and military, may not be that critical as each individual patient has an incidence of 100%. So total population TBI incidence and prevalence in the military relate more to the research needed for healthcare planners who have to find ways to fund the care needed by these warriors who have given their bodies and minds for our country. But the therapeutic approaches to these two groups of patients need to be different depending on the level of TBI and any associated physical trauma.

Blast TBI

As reported above, civilian causes of TBI include falls, personal assaults, and motor vehicle accidents. These causes also exist in the military, from training exercises, bar fights, and especially motor vehicle accidents probably due to the age range of the military population where these incidents tend to occur at a higher rate (20-24 years of age).

However, the unique cause of combat TBI is exposure to blast from improvised explosive devices (IEDs), rocket-propelled grenades, and mines. "Blast is overwhelmingly the most common wounding etiology in the current conflicts" (Warden, D., 2006, p. 400) and "military sources report that approximately two thirds of army war zone evacuations are due to blast" (Ibid, 2006, p. 399, citing Army Medical Department statistics for 2006). More recent data indicate that explosive mechanisms accounted for 78% of injuries (Owens, B., et al, 2008).

Since interest has been increasing about the high percentage of TBI cases from blast exposure, a great deal of basic and clinical research has been done to tackle the question of does blast create a different form of TBI compared with blunt head trauma or just penetrating wounds. Over the past few years as the existing literature on the effects of blast on animals and humans has been reviewed, and specific animal experiments have more seriously investigated brain tissue damage from blast, there has been a trend to using a more descriptive term for blast TBI to distinguish it from non-blast TBI and the subsequent clinical sequelae. The term used to describe this form of TBI now is Blast Induced Neuro-Trauma (or Neurotrauma), i.e., BINT.

The basic physics of a blast is well known and has been studied for decades. A blast wave generated by an explosion begins as a single pulse of increased air pressure followed within milliseconds by a negative pressure, or suction. The blast wave is a sphere of compressed and rapidly expanding gases and travels faster than the speed of sound and damages surrounding structures in a few milliseconds. Consequently, a soldier exposed to a blast will not only experience the blast wave but also the high-velocity wind that travels immediately behind the blast wave. If the blast occurs in an area with walls and hard surfaces, the effect can be multiplied two to nine times due to shock-wave reflection. "The magnitude of damage from the blast wave depends on five factors: (1) the peak of initial positive-pressure wave; (2) the duration of overpressure; (3) the medium of explosion; (4) the distance from the incident blast wave; and (5) the degree of focusing because of confined area or walls" (Cernak, I., et al, 2010, p. 257).

"Explosions may cause four major patterns of injury: primary blast injury caused by the blast wave itself, secondary injury caused by fragments of debris propelled by the explosion, tertiary injury due to an acceleration of the body or parts of the body by the blast wind, and flash burns due to transient but intense heat of the explosion" (IOM, 2009, p. 33, citing Mellor, 1988).

The most vulnerable parts of the body to primary blast injury are considered to be those with air-fluid interfaces, particularly the lungs, bowel, and middle ear (with rupture of tympanic membrane the most frequent injury). Originally no consideration was given to effects on the nervous system as neurological impairments were thought to be rare due to the belief that the skull provided excellent protection for the brain in these situations. As recently as 2006 Taber reported "a still unresolved controversy is whether primary

blast forces directly injure the brain. Shear and stress waves from the primary blast could potentially cause traumatic brain injury (TBI) directly (e.g., concussion, hemorrhage, edema, diffuse axonal injury). The primary blast can also cause formation of gas emboli, leading to infarction" (Taber, K.H., et al, 2006, p. 143), with the most common types of TBI being "diffuse axonal injury (in gray-white matter junctions especially the frontotemporal regions), contusion (in the superficial gray matter of the frontal and temporal lobes), and subdural hemorrhage (in the frontal and parietal convexities)" (Ibid., p. 144).

"Interestingly, despite several detailed reports published in the 1940s portraying neurological symptoms in soldiers exposed to blast and describing underlying clinical findings and morphological changes in the brain not seen before, the medical community ignored the pre-existing knowledge and attributed neurological impairments due to blast to rare cases of air emboli in cerebral blood vessels" (Cernak, I., 2010, p. 1).

"Nevertheless, accumulating clinical and experimental evidence show that systemic and local alterations initiated by blast significantly influence the brain's response, thus contribute to the pathobiology of acute and/or chronic deficits due to blast" (Cernak, I., 2010, p. 2). Animal studies have shown the effect of blast on the autonomic nervous system (with reduced blood pressure due to vagal nerve reflex, bradycardia, peripheral blood vessel dilation, all leading to cerebral hypoxia.), on energy metabolism (due to effects on the sodium pump that regulates ion transfer across cell membranes), and on levels of circulating hormones. These insults have resulted in reduced animal brain activity (using EEG studies) and memory and performance deficits. "BINT represents a unique clinical entity caused by interwoven mechanisms of systemic, local,

and cerebral responses to blast exposure" (Cernck, I., et al, 2010, p. 258) but "currently available literature is contradictory and often misleading" (Ibid., p.262).

The long-term effect of BINT is not clear. Will it follow the same path as TBI from the usual mechanical force (whether mild, moderate, or severe), or will it have a unique set of sequelae? "What is less clear is the degree to which long-term effects can be caused by a primary blast wave sufficient to produce MTBI and whether multiple exposures to this type of blast, which is common among troops in Iraq, can lead to significant long-term injury" (Elder, G.A., Cristian, A., 2009, p. 113). Another confounding factor is the prevalence of posttraumatic stress disorder (PTSD) in warriors from Iraq and Afghanistan. "The relationship between MTBI and PTSD is interesting because the 2 disorders can in one sense be considered different ends of a spectrum, with TBI the classic example of an organic brain disease and PTSD being a psychologically based reaction to a stressor that was not associated with physical injury" (Ibid., p.115).

With warriors having a range of symptoms that often meet the criteria for both diagnoses, they may prefer to be labeled with the organic version of the condition, just as WW I soldiers preferred to have 'shell shock' as a neurological diagnosis. For warriors wanting to avoid the 'stigma' of having a 'mental health condition' and preferring to wear their wounds honorably, TBI is a more acceptable diagnosis. "Furthermore, a clear-cut distinction between physical and psychological injury is unlikely to be realized, not least because the two coexist" (Jones, E., et al, 2007, p. 1644).

Pathobiology of TBI

While not the main focus of this paper, i.e., the impact of TBI on executive function, a general understanding of the pathobiology of TBI, and especially blast TBI (or BINT) is worth exploring.

The damage to the brain from the initial mechanical trauma is only the beginning of the pathological process. Following the initial trauma a series of secondary cascades are activated that affect the course of progression of the primary damage. It is generally accepted that there are four phases to the pathobiology of TBI. Phase 1 is "the initial mechanical damage that results in rupture of cellular and vascular membranes, release of intracellular contents, and cessation of blood flow. Impairment of cerebral blood flow and metabolism leads to anaerobic glycolysis and accumulation of lactic acid. Energy-dependent membrane ion pumps fail and adenosine triphosphate (ATP) stores become depleted" (IOM, 2009, p. 19). The actual damage in any TBI is also a function of the type of wound, the extent of the wound, and the demographics of the patient. Phase 2 "involves the progressive deterioration of the neural axis that arises from biomechanical and molecular events that collectively promote necrotic and apoptotic cell death" (IOM, 2009, p. 20). "In Phase 3, secondary events – such as hypoxia, hypotension, ischemia, increased intracranial pressure (ICP) and brain swelling, and metabolic failure – perturb brain function further and augment cell injury" (IOM, 2009, p. 24). Phase 4, which represents recovery and improving functional outcomes "is influenced by primary and secondary injury responses and by wound-healing events, including phagocytic removal of cellular debris, glial scar formation, and plastic changes in neural networks" (IOM, 2009, p. 24).

Other elements of TBI relate to whether the damage is focal (i.e., brain damage due directly to the forces impacting the skull) or diffuse (i.e., related more to acceleration and/or deceleration of the brain rather than direct impact on the brain). Obviously there is overlap depending on the actual traumatic event. Focal injuries result in lacerations, contusions and hematomas, plus ruptures of cortical blood vessels, plus direct neuronal injury. "Four pathologic conditions have been attributed to diffuse TBI: traumatic axonal injury, hypoxic brain damage, brain swelling, and vascular injury" (IOM, 2009, p. 26). Probably the most important predictor of eventual outcome comes from the course of resolution of axonal swelling. While actual severing of cortical axons is rare, axonal swelling affects the permeability of the neurons, which then affects axonal transport.

Some aspects of the course of blast TBI have been discussed above. But the key issue is that "primary blast injuries are characterized by the absence of external injuries and by potential parenchymal damage, mostly of the lungs; thus internal injuries are often unrecognized, and their severity underestimated" (IOM, 2009, p. 33). Blast injuries are usually part of polytrauma that involves multiple organs and sensory systems, such that internal bleeding can affect blood flow to other organs including the brain. But the primary impact of blast TBI, or blast-induced neurotrauma (BINT), is quite different from that of mechanical TBI. While it was once thought that the skull provided excellent protection for the brain, with any brain damage being due to air emboli in the cerebral blood vessels, this is no longer accepted. Instead, it is now believed that "BINT can develop without a direct blow to the head and results from the kinetic energy transfer of the blast wave through large blood vessels in the abdomen and chest to the central nervous system. As the front of the blast overpressure interacts with the body surface and

compresses the abdomen and chest, it transfers its kinetic energy to the body's fluid phase. The resulting hydraulic interaction initiates oscillating waves that traverse the body at about the speed of sound in water and deliver the kinetic energy of the blast wave to the brain. Once delivered, that kinetic energy causes both morphologic and functional damage in distinct brain structures" (IOM, 2009, p. 37).

How all of these approaches affect cognitive functioning, and in particular executive functioning, and how any damage can be rehabilitated is the focus of the balance of this paper.

B. COGNITIVE ISSUES

Cognition

"Cognition, or mental activity, describes the acquisition, storage, transformation, and use of knowledge" (Matlin, M.W., 2009, p. 2). To try to relate changes in executive function to TBI, especially due to combat, an understanding of the elements of cognition and how these relate to the central executive, and how it operates, is necessary. This also has clinical importance, as a deficit in executive functioning is identified by changes in performance on standardized tests of cognitive functions, and rehabilitation requires the use of cognitive ability. Likewise, therapeutic interventions for comorbid psychopathology, such as PTSD, require cognitive ability to 'think through' (i.e., acquire, store, transform, and use knowledge) so that cognitive restructuring of the traumatic incidents that caused the PTSD, and its ongoing symptoms, can be achieved.

Relevant Components of Human Cognition

The study of memory is one of psychology's most difficult areas of research, and yet it is the human attribute that is at the root of cognitive dissonance, psychological distress, and emotional disturbance, while also being the basis of one's intellect, personality, and developmental stability. With such importance, it has long been a major preoccupation for those who have attempted to more accurately understand the wide variations in human mental processing. The memories of both the subject/patient and the researcher/clinician are variables in any research or clinical interaction. While objective behavioral outcomes can be measured directly, all subjective outcomes are dependent on memory at some level.

The research on memory by Hermann Ebbinghaus (1850-1909) was the first attempt at studying higher mental processes, and at the time when the prevailing wisdom was that this was impossible to do. Yet Ebbinghaus, probably due to his isolation from major centers of psychological research (especially Leipzig and Wilhelm Wundt) "became the first psychologist to investigate learning and memory experimentally" (Schultz & Schultz, 2008, p. 106). He carried out his experiments on himself, as he had no students, laboratory, or academic appointment. He created a "meaningless series of syllables" (Schultz & Schultz, 2008, p. 109) as lists to be memorized. Interestingly, and incorrectly, this has been translated in some of the literature as 'nonsense syllables' yet it was not so much the lack of sense of the syllables themselves that was important, but the total string of syllables that had to be memorized. The point of this string of syllables that made 'no sense' was to measure learning without the contamination of prior

knowledge and experience. He attempted to measure pure memory without any context or association.

He created a supply of 2,300 syllables to be used in his lists, and carefully measured how his ability to learn series of these syllables compared to learning other materials with association and meaning. He found that it took about nine times longer to memorize a list of 'nonsense syllables' than it did for a similar length of prose that had literal meaning. He also studied the effect of forgetting, and was able to quantify the degradation of memory using these lists, showing a dramatic drop-off of about forty percent in the first 20 minutes, and about half of what was memorized is forgotten in the first hour, followed by a gradual reduction to some steady state of memory after about nine hours. This is his famous 'forgetting curve.' While a breakthrough in experimental psychology of memory and learning, this had little ecological validity as the conditions in which the research was conducted [were] not similar to the natural setting where the results [would] be applied (Matlin, M.W., 2009, p. 12).

William James (1842-1910), who also was not influenced by the prevailing structuralism of Wilhelm Wundt and the Leipzig school, took a completely different approach to psychology. While he was one of America' greatest philosophers he was not an experimentalist, and so his writings were conceptual rather than experimental. He believed that "the goal of psychology is not the elements of experience but rather the study of living people as they adapt to their environment" (Schultz & Schultz, 2008, p. 187). "His idea was that we do not need to remember every piece of sensory information we are exposed to, as this would overload us with trivial data." He also suggested that we have "two memory systems; 'primary memory', a system that allows us to experience

consciousness; and 'secondary memory', a system that allows us to store events from the past" (Moxon, D., 2000, p 4). These concepts later became established as short-term memory (STM) and long-term memory (LTM). James' approach does have a level of ecological validity as it was based on what people did in everyday life, not the very controlled experimental and measurement environment of Ebbinghaus, which is not at all how people use memory in normal daily living. In particular, James' rejection of introspection (and structuralism) as a valid way to understand the inner-workings of the human mind was a basis for the cognitive approach. He believed that there were valid internal processes and that these account significantly for the individual experiences of human beings, in contrast to the social uniformity of responses to stimuli later promoted by behaviorists.

In addition to memory storage capacity, the concepts of top-down and bottom-up processing are key aspects of how we recognize objects that we use on a daily basis. While perception comes from a stimulus being received by a sense organ (e.g., retina of the eye and the information being processed up to the visual cortex), it can be modified by information coming 'down' from higher cortical centers to impact on the overall processing of information due to "the influence of concepts, expectations, and memory" (Matlin, M.W., 2009, p. 24). These two processes work in tandem at all times, and allow us to avoid a sensory overload from all the incoming stimuli that we receive every minute of the day, and they work together to create a very fast and accurate process of dealing with information coming in and being evaluated based on our past experiences. By using experience and expectations to modify the incoming bottom-up information as it arrives, top-down processing allows us to concentrate on the major (or important) information

facing us. Bottom-up observation is more frequently used in contexts where stimuli are unfamiliar or where previous expectations have not caused any immediate assumptions. So more deductive reasoning, based on context and detail, will often be required to achieve a meaningful interpretation of one's observations, and bottom-up processing is a more directly physical experience with an object of interest.

However, it was not until many years later that serious experimental investigation of short-term memory was initiated with the classical publication by George Miller in 1956, in which he proposed that we are able to hold seven plus or minus two (7+/-2) items (or 'chunks') of information in short-term memory (Matlin, M.W., 2009). The research that followed moved beyond his original hypothesis and the techniques used showed that "the material held in memory for less than a minute is frequently forgotten" (Matlin, M.W., 2009, p. 97). Additional data on the effect of the position of a word in a sequence of words demonstrated a variation in recall depending on whether the words were at the beginning of a sequence (primacy effect) or at the end of a sequence (recency effect). Other variables in these short-term memory experiments using words were the pronunciation time (i.e., a function of the length of the words that would be verbalized) and semantic similarity (i.e., the effect of a word's meaning can affect storage time). Other data showed how short-term memory can be interfered with, by adding confusing information to the sequence of memory tasks.

"The most influential two-component model was that of Atkinson and Shiffrin (1968), who proposed that information came in from the environment into a temporary short-term storage system which served as an antechamber to the more durable LTM. In their model, the temporary system also served as a working memory, a workspace

necessary not only for long-term learning, but also for many other complex activities such as reasoning and comprehension" (Baddeley, A., 2003, p. 190).

The Central Executive

The next conceptual breakthrough about the interactions that occur before information is stored in long-term memory came in 1974, when Baddeley and Hitch expanded the STM model to take into account certain research findings regarding a string of random numbers that had to be rehearsed in order while at the same time performing a spatial reasoning task, a phenomenon the sequential Atkinson & Shiffrin model could not explain. "Specifically, this study suggested that people can indeed perform two tasks simultaneously - for instance, one task that requires verbal rehearsal and another task that requires visual or spatial judgments" (Matlin, M. W., 2009, p. 106).

This led Baddeley and his colleagues to propose a more complex structure for STM, which they called working memory (WM) and composed of 1) a visuospatial sketchpad to hold visual information, 2) a phonological loop to hold auditory information, and 3) a central executive function that, while not storing any information, would operate the system efficiently and allow both enhancement and suppression of information so that the mind could stay on target and focus on tasks, and not be distracted by all the other incoming extraneous information from sensory input and feed-back from long-term memory. In 2000 a fourth component, an episodic buffer, was added to account for later research findings, which "is assumed to be a limited-capacity temporary storage system that is capable of integrating information from a variety of sources. It is assumed to be controlled by the central executive, which is capable of retrieving

information from the store in the form of conscious awareness, of reflecting on that information and, when necessary, manipulating and modifying it" (Baddeley, A., 2000, p. 421).

However, it is the central executive that seems to be the critical element in the model as "it almost certainly is the most important component in terms of its general impact on cognition" (Baddeley, A., 1996, p. 5). This is the unique aspect of the Baddeley model as it proposes an active element that controls and organizes, and even inhibits, information gathering into memory and human functioning. It helps us focus our attention, develop strategies for working and daily living, and suppress unnecessary information to the task at hand. However, unlike the other three elements it does not 'store' information. It is the 'boss', i.e., it does nothing useful - other than making sure the other three elements (employees) are doing what they should be doing, and also strategizing for the future!

During the same period that Baddeley was conceptualizing the central executive, others were also working to explain cognitive abilities to deal with novel, non-routine, tasks. The Supervisory Attentional System (SAS) was one such original process that was based on a model that was more complex that the central executive of Baddeley, and originated from work in artificial intelligence. The SAS was considered to be a limited capacity system and used for a variety of purposes, including: tasks involving planning or decision making; trouble shooting in situations in which the automatic processes appear to be running into difficulty; novel situations; dangerous or technically difficult situations; and situations where strong habitual responses or temptations are involved (Shallice, T., 1982). For the purposes of this project, Baddeley's central executive model

is considered to be more easily understood and applicable to clinical findings and conditions, especially these relate to combat TBI.

Since the concepts of the 'central executive' and 'executive function' (or 'executive functioning') were formulated a great deal of research has been carried out to try to measure the impact of these elements in several aspects of memory and cognitive activities. One group of prominent researchers has proposed that the term 'executive function' is too broad, based on its neurological linkages, and it might be better discussed and researched in term of 4 sub-domains: executive cognitive, behavioral self-regulation, activation-regulatory, and metacognitive. They also suggest that the other aspect that seems to dominate these different areas is the role of self-awareness. "Currently available tests of EF typically lack specificity, even when they are sensitive" (Cicerone, K., et al, 2006, p. 1215). Therefore these authors call for new tests that address each of the 4 domains. And they clearly differentiate between treatments designed to address (and ameliorate) executive process impairments with strategies designed to simply compensate those impairments. For example, they indicate that (in 2006) "there are no medications that currently meet a practice standard for treatment of executive deficits in TBI, or, for that matter, any other cognitive impairment in this population" (Cicerone, K., et al, 2006, p. 1216).

Another group studying cognitive impairment after TBI looked at whether this is due to a general slowing of perceptual, motor, and cognitive activity (processing speed hypothesis) or, instead, is due to an impairment of the central executive system of working memory (WM hypothesis). The authors conclude that their research supports the WM hypothesis over the speed-processing hypothesis and "that TBI mainly causes an

impairment of the CES and that this impairment, rather than a speed processing deficit, can be the mechanism underlying deficits in WM, divided attention, executive functions and LTM" (Serino, A., et al, 2006, p. 29-31). As no differences in WM performance was found based on location of lesions, they concluded "that CES functioning is sustained by a distributed cortical network, involving also parietal and temporal cortex, rather than by a unique frontal region" (Serino, A., et al, 2006, p. 31).

Assessment of Executive Function

Thus, the research carried out and reported since the Baddeley model was proposed has expanded the understanding of executive function, with the recognition that because it is multidimensional, like memory itself, it is difficult to measure in both a clinical and research setting. It is a particularly individual aspect of behavior, especially when faced with novel and non-routine situations requiring judgment. Most standardized tests are carefully structured, and the patient or subject is told what the rules are, such as what to do and how much time to do it in. "Since executive function covers a wide domain of skills, there is no agreed-upon 'gold standard' test of executive function. Rather, different tasks are typically used to assess its different facets" (Banich, M.T., 2009, p. 89). Given the many aspects of executive function (planning, organizing, initiating, monitoring, and adapting behavior) it is no wonder that there is no single test that can assess all of these different attributes. This is a more complex measurement than of IQ where the Wechsler Adult Intelligence Scale (WAIS), or one of its evolved forms, is widely accepted as reliable and valid instruments for this purpose. Also, as executive function is one element of working memory, aspects of memory and attention (and the

visuospatial sketchpad and phonological loop) add to the difficulty to focus on executive function alone.

In an initial review of the literature several tests appear frequently in the research articles that address executive function; i.e., the Wisconsin Card Sorting Test (WCST), the Tower of London Test, and the Stroop Test. These well-established tests are supported by a body of research into a number of neuropsychological conditions, including changes in executive function. However, a study published in 2005 (Rabin, L.A., et al, 2005) based on data collected in 2001, provides a quantitative summary of the actual use of the different tests available to neuropsychologists to assess executive function, memory, and attention, as well as more general data on all neuropsychological tests used. This study was based on a survey of 2,044 randomly selected members of APA Division 40 (Clinical Neuropsychology), the National Academy of Neuropsychology (NAN), and/or the International Neuropsychological Society (INS) based on their 2000 membership directories. Only those with doctoral degrees and residing in the US or Canada were included. The sample of 2,044 was randomly selected from a total of 5,840 members from the three membership organizations. The questionnaire was in two parts: 1) demographic information and most frequently used assessment instruments; 2) responses to test used for a vignette about a TBI patient experiencing cognitive difficulties. Of the 879 survey returns (44% response rate), 132 were unusable for several reasons, so the final number of responses was 747 (i.e., 40%). The doctorates of the responders were PhDs (87%), PsyDs (9%) and EdDs (3%), with designated practice identities of clinical psychology (62%), counseling psychology (11%), clinical neuropsychology (11%), school psychology (5%), and neuroscience (2%).

Mild head trauma was second only to depression for frequency of clinical work, with severe head trauma, in the ninth position ahead of personality disorders, bipolar disorder, and substance abuse. Sixty-two percent of the responders were in private or group practice, 34% in medical hospitals, and 17% in rehabilitation facilities. Executive functions were assessed most frequently after attention and verbal memory. A vast majority (68%) of responders favored a flexible battery approach. The most frequently used test of all identified for any specific cognitive assessment was the Wechsler Adult Intelligence Scale (Revised and III).

The responses to the TBI vignette were especially interesting relative to this paper. For executive functioning 219 tests were identified as being used, 56 of which exclusively for executive functioning, and the top 40 were ranked for frequency of use. The most frequently used instrument to assess executive functioning was the Wisconsin Card Sorting Test (WCST) with 75.5% of the respondents indicating its use as at least one of a battery of tests. The top ten are listed below based on frequency of use by respondents. It was surprising to find that many on this list were not used in the well over 150 research articles on executive function reviewed for this project. The fact that 219 tests were being used by 747 clinicians to assess executive function suggests that some are probably 'home made' and used only by the person who created them. Whether an assessment of the validity and reliability of the tests has ever been carried out is doubtful. And this is within a population of doctoral level clinicians who are members of neuropsychological professional societies.

However, this survey was carried in 2001, and several new tests that are being reported in the recent literature (since 2007) had not been created then. Also, the

potential for those in private/group practice (the majority of respondents) to use tests of personal choice rather than with proven validity and reliability is likely to be more often the case than for researchers and academics who create the bulk of published articles on executive function. The survey will be carried out again in 2011, so new data should be available in a few years. It will be interesting to see then how this ranking has changed (Rabin, L.A., 2010, personal communication).

The top ten assessment instruments used for evaluating executive function in 2001 were (Rabin, L.A., et al, 2005, p. 57), with the percentage of respondents indicating use, were:

1. Wisconsin Card Sorting Test (WCST) (75.5%)
2. Rey-Osterrieth Complex Figure Task (ROCFT) (41.0%).
3. Halstead Category Test (40.1%)
4. Trail Making Test (39.8%)
5. Controlled Oral Word Association Test/FAS (COWAT) (23.5%)
6. Wechsler Adult Intelligence Scale-Revised/Wechsler Abbreviated Scale of Intelligence-Block Design (WAIS-R/WAIS-III/WASI-Block Design) (22.8%)
7. Wechsler Adult Intelligence Scale-Revised/Wechsler Adult Intelligence Scale-III Neuropsychological Instrument (WAIS-R/WAIS-III) (17.0%)
8. Stroop Test (16.8%)

9. Wechsler Adult Intelligence Scale-Revised/Wechsler Adult Intelligence Scale-III-Picture Arrangement (WAIS-R/WAIS-III Picture Arrangement) (11.9%)

10. Porteus Maze Test (11.6%)

Other assessment instruments that are routinely reported in the current literature for executive function assessment include the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A) (not listed), the Behavioral Assessment of the Dysexecutive Syndrome (BADS) (which is listed in 40th position for 2.0% of respondents for EF), the Tower of London test (15th position for 6.9% of respondents for EF), the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (listed 23 for all neuropsychological assessment instruments used by 2.1% of respondents, but not listed in the top 40 for executive function) and Profile of Executive Control System (Pro-Ex) (not listed). Tests closely associated with the assessment of TBI in the military were not included, as they are not directly aimed at assessing executive function. These include the Warrior Administered Retrospective Casualty Assessment Tool (WARCAT) and the Automated Neuropsychological Assessment Metrics (ANAM). This latter computer-based self-administered test takes about 20 minutes and is now being used for pre-deployment (for baseline data) and post-deployment assessment for TBI and other neurological deficits from combat operations.

As these data are from a survey of mostly private/group practitioners one question that needs to be addressed is, what is the frequency of tests in the literature by people presumably who have a greater grasp on the validity and reliability of different tests for different functions as they take these issues seriously. For example, just because the

ROCFT (originally developed in Switzerland for children with TBI) is in second place does not mean it is any more useful for evaluating executive function than other more recent tests, such as BRIEF-A and BADS (see below). Another explanation could be that either academics who do the research do not think highly of ROCFT or have no direct experience with it, while those in real-world practice find it useful based on experience and clinical intuition. Of particular interest to this project are two tests mentioned above that were developed to explicitly evaluate executive functioning.

The first of these, the Behavioral Assessment of the Dysexecutive Syndrome (BADS) test, was developed in the 1990s by several experts in executive function research to specifically assess executive dysfunction (i.e., Baddeley's dysexecutive syndrome). This led directly from the work of Baddeley as one of the authors was one of his colleagues and was involved in the original work that conceptualized the central executive system. The creators of this test recognized that patients might perform well on specific tests but still not be able to function in the real world, as most neuropsychological tests typically look at the building blocks of the cognitive skills, whereas patients might not be able to put it all together in normal tasks requiring executive functioning. There are 6 subtests that are administered by a trained administrator (Rule Shift Cards Test, Action Program Test, Key Search Test, Temporal Judgment Test, Zoo Map Test, and Modified Six Elements Test). In addition there is a 20-item 'Dysexecutive Questionnaire' (DEX) that patients and caregivers (e.g., relatives) complete. A profile score is calculated for each test, and an overall profile score of all tests is converted to a standardized score allowing classification into a performance category (Wilson, B.A., et al, 1998). An independent evaluation of the BADS test from

all aspects, noted that the full test takes approximately 30-45 minutes without the DEX, with scoring adding another 15 minutes. The conclusions were that "these tests do appear to present demands that are more naturalistic than those of traditional measures while retaining a format that enables standardized scoring. The tests have also achieved a respectable degree of construct and concurrent validity. The most impressive finding as that, while still modest, the BADS tests have a higher ecological validity than established tests" (Chamberlain, E., 2003, p. 36).

Of direct relevance to this project, a study evaluated the potential for using only the DEX component (the 20-item questionnaire) to effectively identify executive dysfunction in an acute rehabilitation setting, using 64 subjects with a range of TBI measures (GCS and PTA). An expanded DEX of 65 items was created, containing the standard 20 items. Each patient was assessed with this 65 extended DEX (eDEX) by: the patient, a family member, a clinical neuropsychologist, and an occupational therapist. The 6 BADS subtests also were administered along with some other standard tests. The conclusion was that the 20-item DEX in the hands of a competent clinician (not a family member or the patient) was found to be sensitive to executive dysfunction. The applicability to military medicine, especially in an acute trauma center, is that "the DEX can be used with some confidence as a screening instrument to identify executive dysfunction in an acute rehabilitation setting, provided it is completed by professional personnel, trained to be sensitive to the cognitive and behavioral concomitants of this disorder" (Bennett, P., et al, 2005, p. 376).

The second test focusing on executive function, the Behavior Rating Inventory of Executive Function-Adult version (BRIEF-A), evolved from a test originally created by

neuropsychologists working with children. The adaptation of the original BRIEF test to become BRIEF-A has allowed this to be used with adults. It can identify subtle executive changes in mild cognitive impairment and significant cognitive complaints (Rabin, A., 2006), and has been identified as one of only as few with appropriate predictive validity and reliability to be used with TBI patients and which also explicitly evaluates executive function performance outside the clinical setting (Gioia, G.A., et al, 2010). BRIEF-A is a self-report (and observer report) measure composed of 75 items with 9 distinct empirically derive scales that measure various aspects of executive functioning: Inhibit, Self-Monitor, Plan/Organize, Shift, Initiate, Task Monitor, Emotional Control, Working Memory, and Organization of Materials. The clinical scales form two broader indices: The Behavioral Regulation Index (BRI) and the Metacognition Index (MI), which together generate an overall Global Executive Composite (GEC) score. Standard scores for all three measures based on a normative sample of 1,050 self-reports and 1,200 informant reports (from care givers). The validity and reliability of the tests have been established.

An important aspect of any neuropsychological test is the ecological validity of the findings. "Studies are high in ecological validity if the conditions in which the research is conducted are similar to the natural setting where the results will be applied" (Matlin, M.W., 2009, p. 50). The same is true of clinical assessments; if they are not measuring attributes in settings in which the attributes are to be applied, then there is poor ecological validity. Tests need to be aimed at real world situations to have real-world meaning. This is a difficult thing to achieve in standardized tests that are designed to compare performance across populations so that conclusions can be made about

population differences, or longitudinal changes in a specific population. But in a clinical setting, all of this careful and standardized environment may not be possible. For example, to spend 40 minutes administering a test to a wounded warrior that has no relevance to his immediate needs to function in his new real world is wasting the time of the clinician and the patient. Typical test administration requires a very controlled environment and exact process of test administration. Yet this is an artificial situation relative to the real-world needs for executive function changes in wounded warriors

Consequently, several researchers have been working to assess the ecological validity of tests and how to make their outcome measurements more valid in the tasks of normal daily living. "If different executive tasks measure different aspects of the dysexecutive syndrome, it makes sense to administer, standardly, a variety of tests rather than relying on just one or two. Moreover the choice of tests can be made on theoretical grounds. It would seem prudent to select a range of tests aimed to cover each of three cognitive factors: inhibition or response suppression, intentionality, and executive memory. In addition, it would appear some clinical interview, questionnaire, or other measure of affective changes is necessary, since these aspects appear not well measured by a number of the currently popular neuropsychology tests of executive function" (Burgess, P.W., 1998, p. 556).

In another more recent paper Burgess and colleagues present a compelling case for the need for new and more ecological valid tests that should be developed on a function-led basis to create tasks that are more 'representative' and 'generalisable' to the real world problems of dysexecutive functioning (Burgess, P.W., et al, 2006). And another group points out that "someone with an executive deficit may have no real world

problems if his or her environment places little demand on this skill. Conversely, even minor executive deficits coupled with a highly demanding environment could cause extreme functional impairment. This highlights the need to assess cognitive demands that would be required of any person to function in the person's everyday environment and match these demands to cognitive test performance in order to accurately predict functional consequences" (Chaytor, N., et al, 2006, p. 218). However, another paper that raised questions about the questionable ecological validity of most tests that are carried out in laboratory settings, quite unlike the real world of living with TBI, compared assessment of moderate to severe TBI patients with both the highest rated test (as indicated above based on use), the WCST, and a test they developed for 'naturalistic measures of attention' and found that the results validated the use of standardized tests of executive function to the natural expression of inattentive behavior (Kim, J., et al, 2005). This study, at least for the relationship of executive function and inattentive behavior, gives us some level of confidence that even standardized tests can be made to 'ecologically valid' if they are used appropriately and selected for a specific cognitive domain.

From the literature review of the far too many tests available to assess executive function (literally at least 219 according to Rabin, A., et al, 2005) it certainly suggests there is a need for the academic and clinical leaders in neuropsychology who specialize in executive functioning research and assessment to collaborate to create a 'standard package' of tests that can be recommended as far as ease of administration, ecological validity, and reliability of measurement. This can be achieved when needed, as shown by the choice of outcome measures for phase III clinical trials of patients with mild to severe

TBI at the National Institute of Child Health and Development-sponsored Traumatic Brain Injury Clinical Trials Network Outcome Measures. For executive function assessment this committee was able to select 9 measures overall, of which three were specifically chosen to measure executive functioning: Controlled Oral Word Association Test (COWAT) (5th on the list of most frequently used tests for this purpose above), Trail Making Test (4th on the list), and Stroop Color-Word Matching Test (8th on the list) (Bagiella, E., et al, 2010, p.378). Again, this selection for an important and expensive clinical trail funded by the National Institutes of Health shows that a consensus can be reached on tests to use, with the slection coming from the top 10 of most used tests by clinicians.

An important follow-up study was done as part of the Rabin, et al, survey specifically to determine if changing the demographics of the TBI patient in the vignette would affect the selection of tests of the responders to the survey. The logic of this was to see if the occupation of a TBI patient affected the selection of subtests in the battery for overall assessment of TBI. The question addressed was "whether certain neuropsychological instruments are optimally suitable (and consequently utilized more frequently) for evaluating patients with particular demographic characteristics" (Rabin, L.A., et al, 2007a, p. 252). Three vignettes were presented; a school bus driver (12 years of education), a police officer (16 years of education), and a doctor (20+ years of education). The data show that less than 2% of all instruments listed by the respondents were more frequently used for specific patients groups. "The fact that neuropsychologists only slightly alter test batteries based on patients' occupational and educational classifications has implications for clinical practice and research" (Rabin,

L.A., et al, 2007a, p. 253). Said more simply, it is clear that not much attention is paid by the vast majority of neuropsychologists to match assessment tests to the actual occupational demographics of patients, i.e., no real concern for ecological validity.

Another study from the data of the survey addressed the utilization rates of ecologically oriented instruments (EOIs) by the respondents, all doctoral-level members of neuropsychology professional societies. "An important aspect of ecological validity is *verisimilitude*, or degree of similarity between data collection methods and skills required in the open environment" (Rabin, L.A., et al, 2007b, p. 728). The ecologically oriented tests were identified by purpose and name. Yet "overall, even the most popular EOIs were vastly less common that top traditional instruments in the areas of memory, attention, and executive functioning (24 to 71% usage as compared to 0.2 to 6%)" (Rabin, L.A., et al, 2007b, p. 736). However, the data did show that those who work mostly in clinical settings that need to relate deficits to rehabilitation options were more likely to use EOIs than those who did not.

Other factors also come into play when using standardized tests that are not often considered. One is the motivation of the subject, and one study found that 'effort' can really affect the data. If patients have a reason for doing poorly on a test (for example if they are challenging workers compensating findings or they are involved in a legal claim for disability) poor effort TBI patients perform worse than good effort patients reminding us that the effort of the subjects can significantly affect outcomes, which needs to be considered for all testing, especially executive function (Ord, J.S., et al, 2010). Also, given the importance of discourse relative to executive functioning, a study of race/ethnicity with TBI patients in three groups (African America, European America,

and Latino Americans) using two different tests (WCST and BADS) found that the WCST is a more useful test to use when race/ethnicity concerns exist in the assessment as it does not show any bias on scoring (Proctor, A. & Zhang, J., 2008).

Another major question that arises when considering the appropriate test or tests to use, is whether tests of executive function are really measuring what their developers believe they are, as it is only when the subject perceives that the immediate task is too difficult to handle through behavioral habits or too important to risk failure that executive functioning really operates. Consequently if the subject does not have a sense of difficulty or risk associated with the testing then maybe executive function is not really being tested. Yet "dysexecutive symptoms are maximally disabling, so identifying any deficiencies is also a top priority in developing long-term goals for treatment" (Schutz, L.E. & Wanlass, R.L., 2009, p. 419). Therefore, an interdisciplinary team approach to assessing executive dysfunction is recommended, as each team member presents different styles and tasks and so present a diversity of situations for sampling real-world settings. What may be a challenging test to one subject may not be to another. "If the individual patient does not regard a particular test as a suitable challenge of motivational salience, its objective properties are irrelevant; it will not elicit an executive behavior sample" (Schutz, L.E. & Wanlass, R.L., 2009, p. 421).

This literature search has been remarkable for unveiling the extent of the neuropsychological tests available for the assessment of executive functioning (and other cognitive skills) while at the same time demonstrating a real lack of consensus in the field of neuropsychology for any practice guidelines on what tests are most valid and reliable (especially ecologically valid) for assessing executive functioning. What is positive

about the literature is that it appears that those papers published in peer-reviewed journals tend to use the top five or six most frequently used (and accepted) tests, typically in combination with each other, or more recently created tests that have been designed with a more ecologically valid approach and focused specifically on assessing executive function.

Neurological and Biological Studies of Executive Function

Some of the most interesting aspects in the study of executive function are the attempts made to try to determine its location in the brain. While Baddeley and other early workers studying executive function never suggested that there would be a single anatomical site, it was only natural that studies would be carried out to determine the neurological basis for this important cognitive domain. Various perceptual and motor functions are defined in regions in the brain, for example the primary visual cortex in the occipital lobe is the location of vision, with associated areas surrounding it that influence visual perception by bringing experience with other aspects of human behavior to bear on the receipt of visual information. Likewise, body movement functions have been mapped out in the motor cortex, comprised of three different areas of the frontal lobe, immediately anterior to the central sulcus (the primary motor cortex, the premotor cortex, and the supplementary motor area) as a homunculus, with point-to-point identity for the movement of different body parts. But the 'location' of the central executive is even more important as understanding its supporting neurological structure (cytoarchitecture) can help researchers and clinicians understand how brain lesions can affect this complex control system on human behavior.

It would be too simple to say it began with Mr. Phineas Gage, but that is as good a place to start as any as he has become an icon in the search for the physical location of many aspects of cognition, including executive function. The Phineas Gage story is well known, even to high school and undergraduate liberal arts students, because of the picture of his damaged skull that appears in many entry-level psychology textbooks. Gage was the foreman of a railroad crew building a line in Vermont, when a freak blast accident propelled a 3-foot long, 13-pound rod into his left cheek that exited at the midline of his skull, resulting in a severe injury to his left, and probably, his right prefrontal cortex. According to the physician who treated him in 1848, he was "25 years of age, of middle stature, vigorous physical organization, temperate habits, and possessed of considerable energy of character" (Harlow, J.M., 1848). This report tells a remarkable story that even with this massive trauma, Gage was lucid and even walked into the room where we would be treated and stay for a little over a month to heal.

This mid-19th century traumatic event is not unlike those that have happened, and continue to happen, to some of our warriors in combat in Iraq and Afghanistan. Even though Gage's physical wounds healed (even with significant loss of brain tissue and his left eye), Dr. Harlow recorded some initial changes to his behavior towards his friends and his lack of apparent concern for his own wellbeing as he regained his strength. However, it was not until 20 years later, and eight years after Gage's death, that he reported that despite Gage's physical recovery he was "fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many

plans of future operation, which no sooner arranged than they are abandoned in turn for others appearing more feasible" (Harlow, J.M., 1868, quoted in Neyland, T.C., 1999, p. 280). This is a clear case of dysexecutive syndrome due to a penetrating TBI.

Such accidents along with ablation later, and then imaging studies, have allowed neuroscientists to map out areas of the brain and, by observing behavioral changes, draw conclusions about the location of this center of control on cognitive functions. The increase in the number of frontal lobotomies to 'cure' psychosis in the years following World War II also provided information on behavioral changes when the frontal lobes were surgically damaged. This procedure became popular due to the overcrowding of mental asylums and the enormous public cost of warehousing patients. As an example of the problem, in 1937 50% of all US hospital beds were psychiatric, and there were 440,000 patients living in 477 American psychiatric institutions, and the annual cost was approximately $1.5 billion (Mashour, G.A., et al, 2005). As no suitable psychoactive pharmacological agents were available until the mid-1950s the only treatment for these patients was surgery. And with the ability to reach the frontal lobes quickly and relatively easily by transorbital frontal lobotomy that did not require traditional intracranial surgery, the standards of practice declined quite rapidly even to the point that physicians with no neurosurgical training were carrying out this procedure. Also, as follow-up neurological studies started to be reported in the scientific and medical literature the efficacy of frontal lobotomies was questioned, and the reported side effects were quite severe. "Inertia, unresponsiveness, decreased attention span, blunted or inappropriate affect, and disinhibition led to the conclusion that the treatment was worse than the disease" (Mashour, G.A., et al, 2005, p. 412). The complexity of the different

neural circuits in the frontal lobes can lead to specific syndromes, not all of which affect executive functioning. Thus it became clear "via these syndromes that higher functions such as executive activity and social control are regulated by the frontal circuits" (Ibid, p. 413).

This work has identified the frontal lobes of the brain as the center of control of emotional functioning, including executive control. We now know that the pre-frontal cortex (PFC) is the location of executive function, but research suggests it is not simply in a fixed location. It is more a series of locations depending on the specific feature of executive function. The "prefrontal cortex – a neocortical region that finds its greatest elaboration in humans – is centrally involved in this process" (Miller, E.K., 2000, p. 59). Also, the PFC is connected with higher-order 'association' and premotor cortices, not with primary sensory or motor cortices and has a unique pattern of interconnectivity with virtually all sensory neocortical and motor systems as well as a wide range of subcortical structures, and probably exerts a 'top-down' influence over other neocortical regions. So understanding PFC organization could provide important clues to PFC functions.

"The PFC is well placed to integrate diverse, high-level representations, and to exert control over various brain systems" (Gilbert, S.J., Burgess, P.W., 2008, p.112). The PFC is very large with variations in cytoarchitecture and connectivity. It has lateral and medial surfaces, with the lateral surface subdivided into ventrolateral, dorsolateral, and rostral regions each with a different function. For example, the dorsolateral PFC is involved in complex functions such as making plans for the future. It also has strong connections with the anterior cingulated cortex (ACC), which is thought to detect the need for control, e.g., when there are competing ways of behaving in a certain manner.

But there is still a lot to learn about the PFC and executive function it supports. Particularly, more needs to be known about *how* things work even though we now know more about *where* they are working. A great deal has been learned over the past 10 years about "which executive functions can be split into various discrete processes, and the ways in which prefrontal cortex can be split into functionally discrete subregions" (Gilbert, S.J., Burgess, P.W., 2008, p.113). Also, "it is known that prefrontal cortex matures relatively slowly, with some parts continuing to develop though adolescence into adulthood" (Gilbert, S.J., Burgess, P.W., 2008, p.114). This is also true of executive function development, based on studies of children through adolescence and into young adulthood (Zelazo, P.D., et al, 2004).

Neuroimaging studies have demonstrated that different executive functions (manipulating and updating of information, dual task coordination, inhibition and shifting processes) not only recruit various frontal areas but also depend upon posterior (mainly parietal) regions. The intervention of similar prefrontal regions in a large number of executive tasks suggests that the central executive functioning (proposed by Baddeley and Hitch) must be understood in terms of different interactions between a network of regions rather than in terms of a specific association between one region and one higher-level cognitive process" (Collette, F. & Van der Linden, M., 2002).

Also studies of changes of performance on executive function assessments can be correlated with axonal degeneration in the prefrontal cortex (PFC). Frontal white matter hyperintensities (bright spots that reflect axonal damage) from a study of MRI changes and age-related perseveration errors on the WCST concluded "it comes as no surprise that the volume of frontal white matter hyperintensities (FWMH) is directly related to

perseveration on WCST" (Gunning-Dixon, F.M. & Raz, N., 2003, p. 1938). "Experimental work with brain-damaged primates (both human and nonhuman), as well as imaging research with healthy humans, indicates that the PFC – and perhaps the dorsolateral area in particular – is necessary for effective WM capacity and aspects of executive attention" (Kane, M.J. & Engle, R.W., 2002, p. 657). In investigations of the effects of hypertension on the brain, revealed that WMH measured using MRI scans, and correlated with 4 cognitive domains (perseveration, working memory, fluid reasoning, and vocabulary knowledge) in subjects with hypertension had smaller prefrontal cortex and underlying white matter volumes and increased frontal WMH compared with age-related non-hypertensive control subjects (Raz, N., et al, 2003).

Another research article studied persistent symptoms after mild-to-moderate TBI by using a computerized test of executive reaction time, some standardized neuropsychological tests, and diffusion tensor imaging (DFI) in the midbrain, to determine what is different about those who suffer a TBI but recover fully compared with those who have persistent symptoms (postconcussion syndrome, PCS). The subjects were two groups of TBI patients, those with self reported continuing symptoms (e.g., headaches, nausea, vomiting, balance problems, slowed or foggy thinking, dizziness, problems concentration, memory problems, etc.) and those reporting no persistent symptoms. Symptomatic patients had: significantly longer mean reaction times and made more errors on the executive reaction time test; had lower scores on the standardized neurological testing (attention, executive function, memory); and higher fractional anisotropy (FA) and lower apparent diffusion coefficient (ADC) in diffusion tensor imaging (DFI) studies. The authors suggest that changes in the midbrain possibly reflect

disruption of meso-cortical tracts important for functions relying on frontal-striatal networks, such as executive functions. "The impaired performance on the Executive RT-Test, lower combined Executive Composite Score, and altered DTI indices together suggest that subtle brain dysfunction may underlie persistent symptoms after mild-to-moderate TBI" (Hartikainen, K.M., et al, 2010, p.771

A study of the effect of mTBI on dorsolateral prefrontal cortex white matter and associated deficits in executive function using diffusion-tensor imaging (DTI) used 20 selected patients with mTBI from an emergency room population, and 20 matched control patients. Two computerized neuropsychological tests (neither of which is among the top valid and reliable measurement instruments) were used to assess executive function on both groups. Imaging was carried out with standard equipment, and the images were analyzed by radiology experts. The group of mTBI patients performed significantly worse than the control group on the assessment of executive function tests. And the imaging results showed significant differences between the patient group and the control group. The imaging data disclosed white matter abnormalities associated with injury to brain neural axons. This confirms that real brain injury still occurs in mild TBI even without any evidence of microhemorrhages. Of importance is that the white matter injury was located in the dorsolateral prefrontal cortex. This ties changes in executive function to damage to neural axons in the dorsolateral prefrontal cortex. The authors suggest that early intervention could prevent further injury by using the diffusion-tensor imaging to help select patients for cognitive rehabilitation therapy (Lipton, M.L.,et al, 2009.

A complex study hypothesized that 1) TBI severity would lead to greater and more distributed brain activation, and 2) lower IQ, older age, and lower educational level would result in increased brain activation. Four groups, 3 based on GCS scores (3-4, i.e., severe TBI; 5-8, i.e., moderate TBI; and 9-15, i.e., mild TBI) and a control of orthopedic injured matched patients without TBI, were assessed with fMRI procedures using visual stimuli. At the same visit for the fMRI studies, each patient was assessed with tests for functional outcomes and depression. Overall the findings showed that lower GCS scores were associated with higher levels of brain activation, and older age resulted in higher brain activation, but there was no difference based on IQ or education level. "Acute TBI severity was related to increased, diffuse brain activation during a visuospatial cognitive control task that included elevated activity within areas thought to mediate cognitive functions such as visual attention and the ability to inhibit pre-potent responses" (Scheibel, R.S., et al, 2009, p. 1459).

Not only is the cytoarchitecture of interest in studying the functions of the prefrontal cortex and its relationship with executive functioning, but the impact of changes in neurotransmitters on executive function has also been studied. In a paper on the literature of animal studies (rat and marmoset) to determine how changing concentration of the neurotransmitters in the PFC (dopamine (DA), noradrenaline (NA), serotonin and acetylcholine) affect working memory, the authors concluded that the research articles reviewed "highlight the specificity of influences that these neurotransmitter systems have on overall prefrontal executive control, acting to promote distinct components of prefrontal processing in a context-dependent manner" (Robbins, T.W. & Roberts, A.C., 2007, p. 157).

And another review article focused on the neurotransmitters at work in attention deficit/hyperactivity disorder (ADHD) as these are similar to problems of executive functioning and are active in the prefrontal cortex (PFC). The most effective treatments of ADHD work by facilitating catecholamine (i.e., dopamine and norepinephrine) actions, and so these are at work in the prefrontal cortex, which also controls executive functioning. "Neuropsychological and imaging studies have shown that PFC functions are weaker in patients with ADHD. As these executive abilities are critical to our success in the fast-paced Information Age, and ADHD symptomology has increasing liability in modern society" (Arnsten, A.F.T. & Li, B-M, 2005, p. 1382). This also emphasizes the importance of maintaining the correct balance of these two hormones (dopamine and norepinephrine) in the treatment of dysexecutive function.

Taking another approach to the biological characteristics of TBI, one paper presented the hypothesis that individuals with TBI and low activity of a specific enzyme polymorphism would perform better on tests of executive functioning than individuals with the high activity enzyme polymorphism. The mechanism is considered to be due to the genetic differences that create different enzyme functions that modulate cortical dopamine neurons in the pre-frontal cortex where the neural components of executive functioning are located. There are two forms (i.e., polymorphism) of the enzyme catechol-O-methyltransferase (COMT) that modulate dopamine neurons and are therefore likely to affect pre-frontal executive functioning. They hypothesized that reduced cortical dopamine, due to high enzyme (COMT Val) activity, should result in poorer executive functioning. Conversely, low enzyme activity polymorphism (COMT Met) should lead to better performance on tests of executive functioning. One hundred and

thirteen veterans were genotyped for the COMT polymorphism. Of the total, 42 were identified as homozygous Val/Val, 25 were homozygous Met/Met, and 46 were heterozygous Val/Met. Neuropsychological tests were administered to assess executive functioning, including the Wisconsin Card Sorting Test (WCST). A significant difference between genotype groups for WCST perseverative responses was found. Veterans with high enzyme COMT activity (hence causing lower levels of dopamine activity) had poorer performance on measures of executive functioning. These finding are comparable to those obtained with schizophrenic patients with the same enzyme polymorphism (Lipsky, R.H., et al, 2005).

Surprisingly, an extensive online search for papers relating evoked cortical potentials, or EEG studies, with executive function testing was not very successful. This could be due to either the words used for the search or the relative lack of this mode of investigation into executive function. The few papers that were found did not relate substantially to the basics of this paper and so are not referenced.

In summary it seems reasonable to conclude that the focus of executive functioning is in the prefrontal cortex (PFC) of the frontal lobes of the brain, with significant linkages to other sensory association areas. When Baddeley and colleagues first proposed the concept of a 'central executive' this naturally led to a search for its anatomical 'home.' But that was never Baddeley's real intent. As he pointed out, even before he introduced the 'episodic buffer' as the fourth 'component' of his evolving model of working memory; "The central executive is not an organ that might or might not exist, but a scientific concept. Part of its function is to separate the analysis of

executive processes from the question of their anatomical location" (Baddeley, A., 1998, p. 523).

However, from a clinically operational viewpoint when facing warriors with severe PFC damage one would expect significant problems of executive functioning, with aspects varying depending on the precise location of the lesions within the PFC (especially the dorsolateral portion). Research will continue to investigate the distributed nature of the neural connections and also the potential for cognitive science to take into account new information that suggests it is more a loosely knit set of functions rather than a unitary cortical activity. But for now, clinically, we can assume that the 'home' of executive function is in the PFC.

C. CLINICAL ISSUES

Clinical Presentation of Executive Dysfunction

The separation of physical and neurological location from the actual cognitive processes is an important aspect of the evolution of this whole area of research, and resulting patient care. "The concept of a 'dysexecutive syndrome' was proposed explicitly to allow a discussion of function to be separated form the question of anatomical location of such functions" (Baddeley, A., 1998, p. 524). Hence the term 'dysexecutive function' has come to refer to the abnormal outcomes from damage to parts of the brain that are responsible for executive functioning. This came from the neuropsychological research base and the eventual understanding that the central executive was not a unitary entity and as other parts of the working memory model have

fractionated, this fractionation of the central executive is not surprising. That is what happens when a functional model is proposed and researchers start to test it. The beauty of the central executive model is not that it is being subdivided, but that it has proven to be accepted as a fundamental controlling system in working memory.

Interestingly, soon after the evolution of the 'dysexecutive syndrome' by Baddeley working in neuropsychological research, a psychiatric clinical group also suggested the same concept, with a slight twist in wording. This resulted from an interesting case study of a 51-year old male patient with Huntington's disease whose "increasingly undirected motor activity, agitation, and disinhibited behavior" led to his admission to an inpatient neuropsychiatry service of a major academic medical center. During his stay in the unit his disruptive behavior (along with his test scores on the Mini-Mental State Examination (MMSE) and the verbal test of Trail Making B) went from bad to worse, then back to bad, and then to better all dependent on the type of psychotropic medication prescribed. The reason this case history is important is it represents a real-world clinical encounter to treat symptoms "that do not fit a classical psychiatric syndrome, such as mania, mood disorder, anxiety disorder, or psychosis" but "are seen at times in patients with TBI, Parkinson's disease, stroke, AIDS, Alzheimer's disease, and frontotemporal dementia" (Lyketsos, C.G., et al, 2004, p. 250). It was not until the group reformulated its approach to deal with 'frontal lobe syndrome' with dopamine augmentation since all the other approaches had failed, that "there was a rapid, almost total resolution of the problem behaviors" within a few days (Ibid, p. 249). The term 'frontal lobe syndrome' has an unclear origin, although it was popular in the 1960s, and there has been little consistency in its use. The problem is that it ties a constellation of

clinical phenomena (i.e., a syndrome) to an anatomical location, when there is no direct evidence that the resulting maladjusted behaviors are solely due to a dysfunction in that location, and could also be due to damage in subcortical structures. Consequently, "the term 'frontal lobe syndrome' is no longer useful because it implies damage to a specific region of the brain" (Ibid, p. 252). The authors proposed a new term, 'executive dysfunction syndrome' to identity "a clinical syndrome – akin to 'psychosis,' 'manic episode,' or 'affective/mood disturbance' – and avoids the use of a pseudoanatomical term ('frontal')" (Ibid, p. 252). These authors also recognized the existing basic science research of several possible circuits originating within the frontal lobes, such as the dorsolateral prefrontal circuit, the lateral orbitofrontal circuit, and the anterior cingulam circuit, with the possible neurotransmitters.

While the debate about a 'dysexcutive syndrome' or an 'executive dysfunction syndrome' still goes on in the research literature, the basic conclusion that can be drawn as it relates to the purpose of this paper is that patients with frontal lobe damage (especially PFC) due to trauma can exhibit any number of serious behavioral and cognitive changes depending on exactly where the lesion is located, and, if the damage is more diffuse, how it affects more than one circuit or region. Given the number of neural circuits associated with executive function, it is not surprising that changes will occur in executive function due to blast TBI. The more important issue is how to identify the level of problem and find associated rehabilitative techniques so that warriors with all levels of TBI can maximize their own cognitive control as they look to the future.

Regarding the specifics of blast TBI and mechanical TBI, one important paper directly assessed whether there are differences in the cognitive outcomes of TBI caused

by blast compared with TBI due to other causes. The study compared performance on some standard neuropsychological tests on 102 Veterans Administration patients (61 exposed to blast, 41 to non blast trauma). A thorough statistical analysis was completed. "Overall the results do not provide any strong evidence that blast is categorically different from other TBI mechanisms, at least with regard to cognitive sequelae on select measures" (Belanger, H.G., et al, 2009, p. 1).

Comorbidity

Throughout this literature review it became clear that depression and posttraumatic stress disorder are often comorbid with TBI. In fact one of the serious clinical issues is to be able to differentiate between symptoms of TBI and PTSD as there are similarities in how these two conditions present. And the very nature of blast TBI creates even more comorbid conditions that need to be assessed.

One aspect of military TBI is the increased emotional distress and other psychological disorders due to the nature of combat. Typically the results of blast TBI includes other polytrauma injuries to face and organs in the head, PTSD and auditory impairments, along with a broader spectrum of injuries associated with pain than come with other forms of TBI (motor vehicle accidents, falls, etc.) in the military. A polytrauma 'triad' of chronic pain, PTSD, and persistent postconcussive symptoms (PPCS) exist in 82%, 68%, and 67% of patients respectively. And the relationship between PTSD and mTBI is complex and could be due to damage to the prefrontal cortex (PFC). "In addition, cognitive or neurobehavioral impairments associated with TBI may influence the efficacy of treatments for PTSD or other mental health conditions" (French,

L.M., 2010, p. 42). Consequently, "a thorough assessment of all comorbid conditions must be undertaken and addressed. For some individuals this can be accomplished in the primary care setting. For others, especially those suffering polytrauma, a specialized program involving neurology, psychiatry, behavioral health, occupational therapy, physical therapy, pain medicine, and other relevant disciplines should be considered for successful treatment" (French, L.M., 2010, p. 43).

One study examined neuropsychological test data to explore the relationship between TBI and PTSD and related measures of processing speed and executive functioning in postdeployed veterans of OEF and OIF, some with TBI only, some with PTSD only, and some with TBI and PTSD. The results suggest that verbal processing speed and executive functioning differ among all three groups. However, PTSD had a greater impact on executive functioning than TBI alone, and the TBI/PTSD group performed worse on verbal processing speed suggesting that the comorbidity reduces the speed of verbal processing than either TBI or PTSD alone. This suggests that treatment for those with comorbid TBI/PTSD may require adapting to include slower verbal processing (Campbell, T.A., et al, 2009).

An important paper on the impact of combat TBI on executive functioning not only addresses real world issues for returning warriors, it also addresses the implications of the findings on treatment options. Processing speed and executive functioning were studied in a group of OEF/OIF veterans with mTBI (58% from blast injury) of which a subgroup also had PTSD. The mTBI patients who also suffered from PTSD scored significantly poorer than those with mTBI only. The authors suggest that clinicians carefully consider whether processing speed slowness may be contributing to

observations and test scores suggesting executive deficits in subacute TBI, especially in veterans with comorbid TBI and PTSD. They also raise the question of whether persisting TBI cognitive symptoms increase the risk for later development of PTSD (Nelson, L.A., et al, 2009).

Another paper studied the relationship between major depression and cognitive impairment (particularly executive functioning) following mild and moderate TBI, as "major depression is a relatively common complication of TBI that is associated with psychosocial dysfunction and postconcussional symptoms" (Rapoport, M.J., et al, 2005, p. 61). They hypothesized that depressed TBI patients would have greater deficits in attention, memory and executive functioning than non-depressed TBI patients. They found that 85% of the depressed group of mild and moderate TBI patients had impaired executive function compared with 53% for the non-depressed TBI patients. Of the total group 28% were identified with major depression. The point prevalence of major depression in TBI patients is between 14% and 29% based on other studies referenced in this paper (Rapoport, M. J, et al, 2005).

In another paper, 91 patients with TBI were studied at baseline, and then at 3, 6, and 12 months after the traumatic incident. Major depression was found in 33% during the first year after sustaining an injury. "Patients with major depression had significantly greater impairment in executive functions than their nondepressed counterparts. "Major depression is a frequent complication of TBI that hinders a patient's recovery. It is associated with executive dysfunction, negative affect, and prominent anxiety symptoms" (Jorge, R.E., et al, 2004, p. 42).

One retrospective study of case records compared blast injured to non-blast injured patients at four Veterans Administration polytrauma rehabilitation centers (PRCs). The purpose was to describe the characteristic and rehabilitation outcomes of patients treated for TBI with polytrauma and other combat injuries. Almost all PRC patients had primary brain injury. The findings indicate that blasts cause more penetrating brain, eye, otologic, skin and soft tissue, oral and maxillofacial injuries, auditory impairments, and PTSD symptoms than other sources of war injuries. The authors found that although patients at low levels of functioning at admissions do not become as functionally independent as those who begin rehabilitation at a higher functional level, they make considerable progress over the course of hospitalization. They also point out that the stay at a PRC is only part of the continuum of care needed to address the lifelong needs of these patients. (Sayer, N.A., et al, 2008).

Consequently, it is clear that blast TBI is accompanied by many other conditions that need simultaneous treatment. So it is necessary to assume that these comorbid conditions exist and to proceed accordingly with every combat TBI patient. The difficulty clinically is to be able to assess these patients for executive function deficits given the more immediate polytrauma that exists. As pointed out in another review paper "although initiating events may differ, there may be a common etiological pathway resulting in the overlapping clinical, symptoms" (McAllister, T.W. & Stein, M.B., 2010, p. 53). The comorbidity may make treatment les effective than would be the case with independent conditions.

A useful paper that ties together data about the sequelae of psychological trauma in service members who received mTBI during combat deployment, also studied whether

there were differences in stress-related symptoms (PTSD) between those with mTBI due to blast compared with those with mTBI who were not exposed to blast. The sample was 724 US military service members (586 with blast-related mTBI and 138 with mTBI from non-blast related sources) over a 4-year span, from a retrospective review of clinical records. PTSD was evaluated using the PTSD Check List (PCL). The blast-related group had more flashbacks and nightmares (re-experiencing symptoms) than the non-blat group. "In summary, there appears to be a significant effect of mTBI on subsequent PTSD symptoms. This effect is greater for mTBI that for other types of injuries, suggesting that there is something about mTBI itself that conveys risk for subsequent PTSD" (Kennedy, J.E., et al, 2010, p. 228). Using a postal survey, 2,235 military personnel were asked about injury mechanisms and the prevalence of mTBI, PTSD and PCS (post concussive symptoms) following deployment in Iraq and Afghanistan. The authors found that 12% reported a history consistent with mTBI and 11% screened positive for PTSD. The strongest factor associated with PCS was PTSD, and combat-incurred mTBI approximately doubled the risk for PTSD (Schniederman, A.I., et al, 2008).

Another review article covered the basic information of incidence and pathophysiology of blast-related injuries, and current Department of Defense initiatives in dealing with TBI associated with these conflicts. "The DoD has established TBI treatment centers based on resource availability. Severe and penetrating injuries are transferred to Walter Reed Army Medical Center or National Naval Medical Center. The exception to this occurs in cases of a polytrauma patient with significant burn injuries. These patients are managed at Brook Army Medical Center" (Jaffee, M.S. & Meyer,

K.S., 2009, p. 1294). Among key efforts under way the authors identify a 15-year longitudinal study of combat-related TBI and a study to validate the use of the Military Acute Concussion Evaluation (MACE) in austere conditions.

Therapy & Rehabilitation

The literature on treatment and rehabilitation of the cognitive deficits caused by TBI, including executive function, is not as well structured or complete as the literature that addresses the physical and mental changes that occur due to the injury. And there are no conclusive clinical guidelines on appropriate treatment protocols. Of interest in any treatment or rehabilitation protocol is the normal recovery process that can occur without any direct intervention. Most mTBI patients recover fully within a few weeks to three months. A study of 75 moderate and severe TBI patients using a multiple battery of neuropsychological tests at 2, 5 and 12 months postinjury assessed the time course of changes in several cognitive functions, including executive function. In general recovery showed an asymptotic relationship for most of the cognitive domains studied, with the most rapid improvement in function occurring in the first 5 months. While there were some limitations in the study this does suggest that aggressing treatment, especially rehabilitation, during the initial months postinjury is warranted (Christensen, B.K., et al, 2008).

Generally the pharmacology treatment of TBI addresses the accompanying symptoms rather than specific cognitive deficits, such as executive function. As there are no FDA approved drugs for the direct treatment of TBI, most pharmacotherapy is 'off label'. One major comprehensive evidence based review of the literature to assess

pharmacologic treatment of all aspects of the sequelae of TBI provides the most complete information to date. A large team of experts undertook a systematic review of the literature in three areas of concern after TBI: affective disorders, anxiety and psychosis; cognitive deficits; and aggression. In evaluating studies of cognitive deficits attention/concentration, memory, and executive functioning were assessed. The authors concluded that there are insufficient data to support a treatment effect for any of the cognitive functions considered in the study. Some clinical guidelines were reported for all aspects of cognitive deficit from general cognitive functions to specific domains like attention and speed of processing and memory. However, few studies on pharmacologic treatment of executive function were found. Dopamine enhancers are the only class of drugs that they identified with suitable evidence level to allow some conclusions. They reported on one class I study that found bromocriptine (Cycloset, Parlodel), a dopamine agonist that activates post-synaptic dopamine receptors, significantly improved measures of executive function in 24 severe TBI patients tested with standard neuropsychological tests, such as the WCST, Stroop Test, Trail Making Test and Controlled Oral Word Association Test. "Bromocriptine is the only medication found to have any evidence in the treatment of executive dysfunction. Executive dysfunction can have significant morbidity with respect to social and vocational functioning and well controlled studies examining possible pharmacologic intervention are much needed" (Warden, D., et al, 2006).

One other study identified by the literature search compared the effect of sertraline hydrochloride (Zoloft and Lustral) on patients with moderate to severe TBI over twelve months compared with a matched placebo group. Test of four domains of

cognitive function (attention and concentration, speed of processing, memory, and executive function) were assessed with standard neuropsychological instruments at 3, 6 and 12 months after admission to the study. No differences were found, and so the hypothesis that sertraline would help aid cognitive and behavioral recovery from TBI was not supported. (Baños, J.H., et al, 2010).

An interesting pilot study on the use of growth hormone in moderate to severe TBI was identified. This was carried out as other studies have suggested that 20% of TBI patients have growth hormone deficiency or insufficiency. Twenty-three subjects were selected for daily injections of either growth hormone or placebo, and cognitive functions were measured using standard neuropsychological tests at baseline, 6 months, and 12 months. Of particular interest are the results of tests of executive function using the Wisconsin Card Sorting Test (WCST). While not statistically significant and therefore no true association could be established, the data suggest a relationship might exist between GH replacement therapy and improved executive functioning. This adds additional information to the neuroanatomical explanations of chronic TBI, and further research is warranted (High, W.M., et al, 2010)

One article described a randomized, placebo-controlled, single-blind study of the effects of acupressure of 8 treatment over 4 weeks on cognitive impairment following TBI. Acupressure is a complementary and alternative medicine (CAM) treatment that uses fingertips to stimulate acupoints on the skin, and can be taught to novices. Given the potential long-term effects of TBI, having a method for self-treatment (like acupressure) could be a major benefit to patients at minimal healthcare cost. The actions of acupressure are unknown, but it has been shown to modulate the autonomic nervous

system and elicit the 'relaxation response'. The impact of active acupressure (vs. placebo acupressure) was studied with the hypothesis that active acupressure treatments would improve cognitive function as measured by standard neuropsychological tests and event-related potentials (ERP). Significant treatment effects were found comparing pre- and post-treatment change between groups. These results suggest an enhancement in working memory function (executive function) associated with active treatments. Further studies are warranted, as this could be a useful adjunct self-care procedure in combination with other more traditional approaches (McFadden, K.L., et al, 2011).

The literature search revealed that most studies of executive function rehabilitation were based on versions of 'cognitive rehabilitation'. One extensive paper looked at 15 carefully selected studies that focused on executive functions of problem solving, planning, organizing and multitasking by adults with TBI. Both careful qualitative (systematic) and quantitative (meta-analysis and assessment of effect sizes) reviews were carried out to assess the effectiveness of metacognitive (i.e., thinking about thinking) strategy instruction (MSI) approaches to treatment with outcomes measured. MSI approaches teach individuals to regulate their own behavior by breaking complex tasks into steps while thinking strategically. Included in MSI approaches were problem-solving therapy (PST), time pressure management training (TPM), concentration therapy (CT), goal management training (GMT) and motor skills training (MST). The study found compelling evidence that training TBI patients using step-by-step MSI will improve problem solving, etc., for personally relevant activities or problem situations. This led the authors to the recommend a Practice Standard, that MSI should be used with young to middle aged adults with TBI for difficulty with problem solving, planning and

organization. The authors point out that a group missing from the studies was combat troops with blast TBI, and best practices in intervention for these patients are unknown (Kennedy, M.R.T., et al, 2008).

Another paper summarized the work in various aspects of cognitive rehabilitation of TBI patients, with evidence ratings. For executive function rehabilitation the Metacognitive Strategy Instruction (MSI) approach, mentioned above, which emphasizes development of metacognitive skills such as problem solving and organization and metacognitive strategies are recommended as a practice standard. The use of 'cognitive prosthetics' or personal data assistants (PDAs) for cognitive rehabilitation support has had mixed results. And pilot studies using virtual reality interventions have yet to show any real impact. The general recommendations made are: 1) use a holistic approach with multidisciplinary teams in the subacute phase; 2) undertake trials of some medications; 3) use specific rehabilitation approaches to attention retaining and retraining of executive function skills; and 4) train patients in the use of supportive devices (memory book or electronic devices) (Cernich, A.N., et al, 2010).

A review article of two previous extensive reviews of the literature on the effectiveness of cognitive rehabilitation for TBI carried out several years earlier by other researchers used a quantitative meta-analytic approach to see if they could reach the same conclusions. They concluded that there was some quantitative evidence to support the two previous systematic reviews by Cicerone, et al. Of the five claims of effectiveness of cognitive rehabilitation within treatment domains, this study supported three (attention/executive, visuospatial, comprehensive). The other two (language and memory) were premature due to inherent problems and uncontrolled research designs.

This is an interesting paper showing how a review of the literature, i.e., analyzing other research papers, can be carried two ways: systematic (qualitative) and metal-analytic (quantitative) (Rohling, M.L., et al, 2009).

One other important review paper brings together the salient information about the efficacy and effectiveness of cognitive rehabilitation for the treatment of TBI. It provides a balanced view of the appropriate neuropsychological tests to use for the most common domains of cognitive functioning assessed post-TBI (intellectual function, memory function, psychomotor speed, processing speed, attention, language, and executive function). For cognitive rehabilitation of executive functioning, they emphasized metacognitive strategies as the most efficacious and effective, using step-by-step procedures to enhance problem solving, planning, organization, and multitasking by increasing the capacity for self-regulation by increased self-awareness (Tsaousides, T. & Gordon, W.A. (2009).

A completely different approach to cognitive rehabilitation was proposed in a paper on the use of neurologic music therapy (NMT). Matched groups (77% and 87% with TBI) went through 4 treatment sessions of a pre-test, 30 minutes of NMT (or rest for the control group), followed by a post-test. The goal was to investigate the effects of therapeutic music training on executive function. Other cognitive domains were assessed also (attention, memory, and emotional adjustment). The training was based on group interactive improvisations, with rhythmic synchronization using percussion instruments based on the therapists lead. Memory was addressed using chants and songs as a mnemonic device. The treatment group showed significant changes in mental flexibility on Part B of the Trail Making Test, with a large effect size, whereas the control showed

no statistical changes with low effect size. These results show promise for NMT to be used to improve executive function in the form of mental flexibility. The large effect size suggests clinical relevance (Thaut, M.H., et al, 2009).

The effectiveness of a group-based attention and problem solving (APS) treatment approach to executive dysfunction in patients with frontal lobe lesions was studied. The basic underpinning was the concepts of Baddeley, and Norman and Shallice. Thirty patients (16 with left frontal and 14 with right frontal lesions) were divided into three groups of 10 each. The APS treatment was compared with treatment-as-usual or traditional rehabilitation and information and education only approach. The first group received APS rehabilitation (10 weeks of 1.5 hours each week concentration on attention and then problem solving, using the metaphor of the mental blackboard for thinking about attention/working memory. "The main treatment approaches to the dysexecutive syndrome described in the literature can be classified as interventions with the aim of: (1) restoring or re-training executive functions; (2) compensating for executive impairments through the use of internal or external strategies; (3) promoting modification of the environment of behaviour by working with carers, family and friends and behaviour modification techniques; and (4) pharmacological treatments" (Miotto, E.C., et al, 208, p. 3)

One paper taking a computer-based approach to cognitive therapy used specially developed online problem solving exercises aimed at executive function training for young patients (11-18) compared with just reviewing online general education about TBI. Families were recruited and balanced to receive either teen online problem solving (TOPS) exercises (stress management, problem solving, planning and organization,

communication, and self-regulation) or just access to online resources about TBI (Internet resource comparison, IRC). The assessment used to measure executive function was BRIEF (for parent evaluation) and BRIEF-SR (for patient self reporting). BRIEF is an inventory of 80 plus items that has been shown to have high levels of internal consistency and test-retest reliability. Teens with severe injuries reported significantly greater improvement in executive function following TOPS that those with severe TBI using IRC, with large effect sizes. This suggests that TOPS may be effective in improving executive function skills among teens with severe TBI (Wade, S.L., et al, 2010). In a similar approach of using computer-based technology, another article looked at the value of a virtual reality kitchen situation and compared performance on a real kitchen setting with similar tasks. Basically the authors showed that the virtual reality kitchen was a valid and reliable substitute for a real kitchen and therefore possibly useful in cognitive rehabilitation (Zhang, L., 2003).

Independent of the actual clinical procedures in CRT, combat injury "the traditional method of connecting diagnosis, sign and symptom presentation, and treatment is difficult to apply when there are multiple simultaneous and cumulative risks, exposures, and diagnoses that are characteristic of polytrauma. Also, symptom presentations are not static but rather dynamic and changing over time and in response to normative life challenges, adding to the difficulty in linking diagnoses to symptoms" (Uomoto, J.M. & Williams, R.M., 2009, p. 261). "Finally, an emphasis on delivering rehabilitation interventions in a compassionate therapeutic milieu characterizes the holistically oriented and patient-centered interdisciplinary team function" (Ibid, p. 263). This provides a counter point to the typical medical model, and is working in many

polytrauma rehabilitation centers (PRCs) dealing with the aftermath of trauma from combat in Iraq and Afghanistan.

Another parameter affecting outcomes in cognitive rehabilitation is self-awareness (SA). The ability to recognize problems caused by damaged brain function is important for the necessary motivation for rehabilitation and safe and independent functioning. One study used 37 patients with severe TBI who were evaluated using neuropsychological tests in attention, memory, and executive functioning. Assessment of SA was done with the Awareness Questionnaire (which was completed by both the patient and a relative who interacted with the patient daily), and assessment of executive functions with the Wisconsin Card Sorting Test, the Tower of London test, and Verbal Fluency. The key measure was the AQ discrepancy score (difference between patient and relative, range –18 to +28). The AQ discrepancy score correlated highly with subsets of the WCST. The authors claim that decreased metagognitive self-awareness is highly correlated with increased problems in some components of the executive system. This strongly suggests the importance of integrating an overall assessment of cognitive functions with a specific evaluation of self-awareness, and also to treat self-awareness within a structured rehabilitation program (Bivona, U., et al, 2008). Another paper raises the issue of impaired self-awareness (ISA) in patients with moderate to severe TBI due to frontal lesions, and how they differ from those with more diffuse TBI and healthy subjects. Of interest are the lower scores on self-reported measures of sickness and higher scores on self-reported measures of recovery towards pre-injury mental status by the frontal injury group, while objective data did not support these personal assessments. This suggests that moderate to severe TBI patients with ISA will think they are doing

better than they really are, and so the observations of other caregivers in their lives (e.g., relatives) become very important in assessing their true status (Spikman, J.M. & van der Naalt, J., 2010).

Finally, a study of the differences in the level of PTSD in soldiers who sustained mTBI from a blast with and without other physical injuries provides some insight into how treating one condition can help in the treatment of a comorbid condition. The authors proposed that "when the patient can focus on demonstrable healing and functional improvement, he or she is reassured about the progress of recovery. The injured person's active effort in the rehabilitation process gives him or her a sense of empowerment and personal fulfillment" (Kennedy, J.E., et al, 2010, p. 195). The authors noted that healing of comorbid physical injuries reduces the relative intensity of PTSD. Hence, the added aspect of recognizing improvements in physical health may enhance the recovery of mTBI as measured by PTSD-like symptoms (Kennedy, J.E., et al, 2010).

Challenges to Cognitive Rehabilitation Therapy

While the effectiveness of cognitive rehabilitation therapy (CRT) for TBI (and specifically executive functioning) has been established in the literature and is the treatment of choice in most clinical centers, this therapeutic approach has recently received challenges, including for military medicine.

A 2009 study commissioned by Tricare Management Agency (the military's health insurance agency) concluded that cognitive rehabilitation therapy (CRT) is scientifically unproved and does not warrant coverage as a stand-alone treatment of brain injuries. The military has requested the National Academy of Sciences' Institute of

Medicine to study the effectiveness of CRT in TBI cases and identify specific treatments that may have enough scientific evidence to warrant coverage by Tricare (Tilghman, A., 2010). The Institute of Medicine has started a yearlong study of cognitive rehabilitation therapy for brain injuries on February 8, 2011 (Miller, T.C. & Zwerdling, D., 2011).

The report that was the basis of the TRICARE decision to not fund CRT was based on several meta-analyses using data from 18 randomized clinical trials. According to the authors of the report, the evidence was too weak to draw any definitive conclusions about the effectiveness of cognitive rehabilitation therapy for treating deficits related to the following cognitive areas: attention, memory, visuospatial skills, and executive function (ECRI Institute, 2011). This challenge to the efficacy of CRT has some support in the private health insurance sector. One major insurance company concluded that based on 5 criteria, cognitive rehabilitation for traumatic brain injury in adults does not meet the TEC criteria (Blue Cross Blue Shield, 2008, May). And, interestingly, a study carried out by a respected research group within the military itself also raised questions about the efficacy of CRT for patients with TBI. The subjects were 120 active-duty military personnel with moderate-to-severe closed head injury. Sixty-seven were randomly assigned to an intensive, standardized, 8-week in-hospital cognitive rehabilitation program, and 53 were assigned to limited home rehabilitation program with weekly telephone follow-up. After one year there was no significant difference between the two groups based on return to work and fitness for military duty as the primary outcome measures. The issue of appropriate outcome measures seems to be at the baser of this controversy. Most of the scientific literature reports on studies showing performance gains on the outcomes of standardized neuropsychological tests. Whereas,

the outcome measures used by this and other studies challenging the efficacy of CRT are more general and practical operational outcomes, such as the ability to return to work, or in the military, to a duty station. One key outcome of the military study was the much lower cost of the home-based program compared with the hospital-based program ($504 vs. $51,840) (Salazar, A.M., et al, 2000). This quantification of the savings could have been what caught the attention of insurance carriers like BC/BS and TRICARE.

However, another major insurance carrier found exactly the opposite. "Cognitive rehabilitation is proven for the treatment of traumatic brain injury (TBI)" (UnitedHealthcare, 2010, p. 1). And a conference of a selected multidisciplinary group of 50 plus subject matter experts from military and governmental departments, addressed the needs of clinicians facing an increasingly large population of wounded warriors who have sustained mTBI and go on to develop chronic symptoms and functional limitations, including cognitive impairment. The group focused on four areas: 1) Assessment, 2) Interventions, 3) Outcome measures, and 4) Program implementation. They developed flow charts of the referral process leading to TBI cognitive rehabilitation. They concluded that "despite the difference in combat related and non-combat related mTBI, there is presently no evidence to suggest that the resulting cognitive deficits are different between the military and civilian traumatic brain injury" (Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury & Defense and Veterans Brain Injury Center, 2009, p. 8). Interventions for executive dysfunction were discussed based on the literature. "Clinical experience with wounded warriors suggests that a comprehensive holistic approach, which provides individual and group therapies within an integrated therapeutic environment, addresses the functional impairment and disability

resulting from cognitive and emotional sequelae of chronic symptomatic mTBI" (Ibid, p. 11). The report also addressed the importance of outcome measures that focus on changes in the ability of an individual to function within an important aspect of daily living, rather than neurocognitive assessment goals that only compare before and after therapy performance on neuropsychological tests.

CHAPTER 3: SUMMARY & CONCLUSIONS

Methodology & Analysis

This project was based solely on a review of the literature mostly published within the past five years and almost exclusively obtained from online sources, by either the author using Google Scholar plus direct communication with several authors for copies of their papers not available online, or by an extensive institutional online search conducted by the library service of the National Naval Medical Center, Bethesda, Maryland. Key words used for all sources included: central executive, cognitive deficits, combat, combat trauma, dysexecutive syndrome, executive dysfunction, executive function, executive functioning, Iraq and Afghanistan, OIF, OEF, TBI, traumatic brain injury. The inclusion criteria applied for papers selected for review were the interest of the reviewer and the apparent usefulness of the article to the topic, with recognition of the quality of the professional journal in which it was published and the credentials of the authors.

Some excellent papers included systematic reviews or meta-analyses of data, and these tended to help weed out inferior papers. However, papers of actual experimental results still made up the bulk of the articles reviewed and referenced. There was no attempt to set any evidence levels in this selection process, as the intent was to obtain an overall view of the topic and not be too limited by whether any single research article had statistical flaws or some other deficit that would lower its evidence rating. It was enlightening to see the same authors' names appearing in the better journals, which led to several email messages to these authors with requests for their papers and comments on

this project. Also using the reference sections of some of the better review articles led to selecting other useful papers to obtain a more complete overview. Of the approximately 200 articles read for this project, 114 were selected as references.

The limitations of this methodology are the already mentioned lack of evidence levels for selected papers and the inexperience of the reviewer.

Summary of Findings

The review of the literature covered areas of study that were not anticipated at the beginning of this project. The working definition of TBI identified with the most efficient use of words is "damage to the brain after trauma (for example, a blow or jolt to the head, a penetrating head injury, or exposure to an external energy source" (IOM, 2009, p. 14). The important thing to recognize about TBI is that it is a physical injury to brain tissue, not a psychological illness. TBI is assigned different forms, i.e., open (with a penetrating wound) or closed, and severity levels, i.e., mild, moderate, or severe. The common term 'concussion' is synonymous with mild (mTBI or MTBI), and TBI severity is categorized most often with the Glasgow Coma Scale (GCS) score and the length of any posttraumatic amnesia (PTA).

From a review of the epidemiology of TBI, we know that 1.7 to 2.2 million people in the US experience a TBI each year, mostly from falls, motor vehicle accidents (with alcohol consumption having an impact), and personal assault, of which 81% are treated in an emergency room and sent home. However, an estimated 125,000 each year will have persistent symptoms and disability. The prevalence in the US is approximately 6 million people, of which 2 million are not receiving any medical care for this condition.

For military TBI the picture is different due to the wars in Iraq (OIF) and Afghanistan (OEF). From 2000 through the end of the third quarter of 2010, 195,000 military personnel had been diagnosed clinically with TBI. Similar to the civilian population, approximately 77-80% were found to have mild TBI (i.e., concussion) with only 2% penetrating, 1% severe (closed head), and 17% moderate. While there are no central databases with accurate information on TBI directly related to combat, population studies of groups of combat soldiers suggest that there are two distinct populations of warriors suffering from TBI. First, those who made it home as functioning soldiers with no apparent injury, yet with the likelihood that approximately 20% were suffering from mTBI (and post concussive symptoms) of which at least 50% are not receiving any medical care. Second, those who were evacuated out of theater and hospitalized due to significant injury, of which approximately 28% were identified with TBI; 60% of which with moderate or severe TBI as a result of their injuries (including 12% due to penetrating head wounds), and the other 40% suffering from mTBI.

There are five neuropsychological symptoms that can be grouped into a systematic classification resulting from combat TBI: 1) cognitive dysfunctions; 2) neurobehavioral disorders; 3) sensory disruptions; 4) somatic symptoms; and 5) substance dependence. But what makes the military population unique is that exposure to blast from improvised explosive devices, mortar, or mines creates 78% of the injuries, the highest percentage for any major conflict, and 66% of all injury evacuations from the theater are caused by blast. Consequently this clinical presentation is now identified as blast induced neuro-trauma (BINT), a unique clinical entity because of these wars.

Unlike mechanical trauma experienced in civilian TBI (and previously in peacetime military situations before OEF and OIF), BINT attacks a warrior in a completely different manner. Explosions cause four major patterns of injury: 1) primary blast injury caused by the blast wave itself; 2) secondary injury caused by fragments of debris propelled by the explosion; 3) tertiary injury due to an acceleration of the body or parts of the body by the blast wind; and 4) flash burns due to transient but intense heat of the explosion. Blast also creates mechanical trauma, similar to that experienced in civilian incidents (by hurling bodies up in the air to fall to the ground or be thrown against walls), and massive acceleration forces on the head causes the brain to move around violently within the bony skull, similar to an automobile accident. A relatively small number of victims also experience penetrating wounds from debris and shrapnel. However, BINT also has a unique feature not experienced in the civilian world.

The kinetic energy of the blast is transferred into the torso and impacts internal organs resulting in intense trauma and hemorrhaging, and then the energy waves are transferred through the major blood vessels and other routes to the brain. BINT attacks the brain from inside the body, quite unlike the impact of external mechanical forces to the head that are the usual causes of civilian TBI. While the pathobiology of mechanical trauma is quite clear, and there is an understanding of the progression of biochemical, vascular, and neurological events that follow, that same level of knowledge about the impact of internal blast waves on the brain, and the long-term effects, are not known at this point. Animal studies are providing some insights into this subject, but while educated speculation exists there are no real data that can help understand the changes occurring in the brain that then cause, and have come to be identified with, specific

cognitive and behavioral changes in the warrior. BINT represents a unique clinical entity caused by interwoven mechanisms of systemic, local, and cerebral responses to blast exposure.

It is generally accepted that there are four phases to the pathobiology of TBI: 1) the initial mechanical damage that results in rupture of cellular and vascular membranes, release of intracellular contents, and cessation of blood flow, leading to anaerobic glycolysis and accumulation of lactic acid; 2) the progressive deterioration of the neural axis that arises from biomechanical and molecular events that collectively promote necrotic and apoptotic cell death; 3) hypoxia, hypotension, ischemia, increased intracranial pressure and brain swelling, and metabolic failure, that perturb brain function further and augment cell injury; and 4) recovery and improving functional outcomes.

The review of the literature on executive function led back to the early experimental work on cognition, and memory in particular. For about 100 years after early studies measuring the amount of information that could be memorized, the concept of two components of memory (short-term memory and long-term memory) was well established. In the 1970s new information challenged this two-component model with the introduction of a 'central executive' by Alan Baddeley and colleagues, which was seen as another component of working memory (formerly short-term memory) along with information storage processing for visual and auditory information. While not storing information, the 'central executive' was proposed to explain how processing occurs in a hierarchical manner so that a human being is able to plan, organize, and prioritize information coming from the external world and from long-term memory based on what is in the best interest of the person at the time, and also including inhibition to prevent

inappropriate actions and behavior. The difference between an adult who has a normal working executive function and one who does not is similar to that of a child under 5 years of age or an adult with ADHD, where behavior tends to be driven by the most recent external stimulus rather than by a careful assessment of what is an appropriate action to a novel event, including avoiding making a bad decision.

While a great deal of research has advanced the concept considerably over the past four decades, there has been no real challenge to the existence of an executive function that allows us to organize and plan our lives. What later research found is that the central executive is not a unitary concept or anatomical entity. There is no 'executive function lobe' in the brain. However, the primary location of activity does appear to be associated with the prefrontal cortex, where a great number of neural projections interact with other areas of the brain that control behavior or receive information from other association areas. That the frontal lobes, which contain the prefrontal cortex, are the most developed in humans also provides a logical 'home' for this critical domain of human cognition that sets us apart from the rest of the animal kingdom. Today's researchers generally agree that the prefrontal cortex is the logical place for the integration of many different and important inputs, and the control of final outcomes. It is known that the prefrontal cortex develops slowly throughout childhood and into young adulthood, which is also the time course for the development of executive function. Over the lifespan, executive function improves over the first two decades of human life, reaches a plateau, and then starts to decline in later years. However, due to the large number of interconnections and the role of the basal ganglia and their relationship to frontal lobe activity, executive function has a very diffuse 'home' with a great many

neural inputs resulting in the unique characteristics of each individual as related to how we each address the challenges and opportunities of life. Executive function is a complex cognitive attribute, and this project has heightened this understanding and acceptance of the behavioral changes in patients with TBI.

The neuropsychological assessment and measurement of executive function has attracted a great deal of attention over many years, initially, as with most tests of cognitive function, in the laboratory. Since the Baddeley model was proposed it has been recognized that it is difficult to measure executive function in both a clinical and research setting because it is multidimensional, like memory itself. The literature is quite extensive, with papers on standardized tests being created and used to examine executive functioning in a range of subjects and in different clinical settings. However, due to its elusive nature, and the growing evidence that many neural networks are actually the basis of executive functioning, it is generally agreed that there is no one 'gold standard' test. While one study identified 219 available tests to assess executive function, most authors published in the recognized scientific journals typically used the same group of standardized tests with documented validity and reliability. The interesting thing about this study is that even when a TBI patient vignette was introduced, the neuropsychologists who responded did not change the tests they would use to evaluate this patient, showing that practitioners appear to be set on the tests they are comfortable with and rely on these for whatever clinical condition they are assessing.

While some of the well-known tests have been identified with adequate validity to measure the cognitive domain intended, and also to produce reliable measurement, there is a legitimate concern that unless tests relate to the ultimate behavioral needs of the

patient simply measuring a specific mental function does not have a great deal of usefulness if it does relate to tasks that person needs to be able to do in his or her own everyday world. Also, as executive function is driven by what to do and when, and to decide on the importance of new information, what might be a challenge for one patient might not be so for another. Consequently, there is a growing movement to create tests that assess executive function in the real-world environment of the individual patient, and within the past few decades a number of tests have been produced that address the importance of ecological validity while focusing specifically on executive function assessment.

From a purely clinical perspective this latter movement is encouraging, and addresses a fundamental issue when dealing with executive function assessment in the military. While the first priority for wounded soldiers is to make sure that they are not medically compromised and have the potential to survive their wounds, the next level of concern is to understand their mental health status, especially if they have suffered a TBI. And this assessment has to be carried out in a time-efficient manner where the potential for several hours of neuropsychological testing is not normally possible, especially when an assessment by a professional is required as opposed to relying on a self-report survey. The identification and diagnosis of executive dysfunction (or dysexecutive syndrome) is the goal of the clinician, not a detailed measurement of executive function itself. The clinician needs to be able to identify that the condition exists and its level of severity. This will then drive any decision for therapy and rehabilitation. The two test batteries that have promise for this are the BRIEF-A test and the BADS test. The latter test has a 20-item Dysexecutive Questionnaire (DEX) that, when administered by a professional

(not the patient or a caregiver as originally intended), has shown to provide a suitable rapid and valid assessment of executive functioning. This could be useful for identifying executive dysfunction in an acute military hospital setting.

The neurophysiological and biological bases of executive function have been studied in number of ways. From the example of Phineas Gage, through ablation studies and a rash of frontal lobotomies after World War II, a great deal has been learned about how lesions in different brain areas affect behavior. With the development of sophisticated digital neuroimaging techniques, a much better understanding of the locus of executive functioning in the brain has been established. This work has helped to confirm that the frontal lobes of the brain are at the center of control of emotional functioning, including executive control. We now know that the prefrontal cortex is the location of executive function, but it is does not exist in a fixed location. It is more a series of locations depending on the specific feature of executive function. Also, the prefrontal cortex is connected with higher-order 'association' and premotor cortices, not with primary sensory or motor cortices, and has a unique pattern of interconnectivity with virtually all sensory neocortical and motor systems as well as a wide range of subcortical structures, and probably exerts a 'top-down' influence over other neocortical regions. Thus it is important to understand that central executive functioning (as proposed by Baddeley) occurs through interactions between networks of cortical regions, not as a specific association between one brain region and one cognitive process.

Also studies of changes in performance on executive function assessments can be correlated with axonal degeneration in the prefrontal cortex, as imaging data have disclosed white matter abnormalities associated with injury to brain neural axons. This

confirms that real brain injury occurs even in mild TBI. And the impact of variations in neurotransmitters on executive function has also been studied showing that modifying the concentration of the neurotransmitters in the prefrontal cortex (dopamine, noradrenaline, serotonin, and acetylcholine) can affect working memory. Also the neurotransmitters active in attention deficit/hyperactivity disorder (ADHD), which displays symptoms similar to those of executive dysfunction, are also active in the prefrontal cortex. The most effective treatments of ADHD work by facilitating catecholamine (i.e., dopamine and norepinephrine) actions in the prefrontal cortex. Also, genetic differences have shown that different enzyme functions can modulate cortical dopamine neurons in the prefrontal cortex. Thus it seems reasonable to conclude that the focus of executive functioning is in the prefrontal cortex of the frontal lobes of the brain, with significant linkages to other sensory association areas, and that the neurotransmitter dopamine is important for normal executive functioning

The clinical presentation of executive dysfunction, also known as the dysexecutive syndrome (Baddeley), are the changes in behavior that result from deficits in planning, prioritizing, and organization skills, along with a lack of inhibition over bad behavior and poor judgments. Typical TBI symptoms include dizziness, difficulty concentrating, memory loss, sleep difficulties, vision problems, vertigo, and confusion. In more sever TBI, vomiting and nausea, slurred speech, seizures and numbness of limbs can be reported. The behavioral changes that can occur, due to executive dysfunction, are difficulty controlling urges (i.e., disinhibition), impulsiveness, inappropriate laughter and irritability, along with clear problems in organizing and prioritizing daily tasks. These latter symptoms tend to become more evident when the challenge to the patient

increases. Hence the basic conclusion that can be drawn is that patients with frontal lobe damage (especially prefrontal cortex) due to TBI can exhibit any number of behavioral and cognitive changes depending on exactly where the lesion is located, and, if the damage is more diffuse, how it affects more than one circuit or region. However, current research suggests there are no differences in the cognitive outcomes of TBI caused by blast compared with TBI due to other causes. There is no strong evidence that blast is categorically different from other TBI mechanisms, at least with regard to cognitive changes as measured so far with standardized tests.

It is clear from the literature that posttraumatic stress disorder (PTSD) and depression are often comorbid with TBI, and one issue is the need to be able to differentiate between symptoms of TBI and PTSD as there are similarities in how they present clinically. And as blast TBI is typically accompanied by so many other physical injuries that need simultaneous treatment, it is necessary to assume that comorbid conditions exist and to proceed accordingly with every combat TBI patient. Patients with both TBI and PTSD tend to perform poorer on verbal processing speed tests, suggesting that it is the comorbidity that reduces the speed of verbal processing rather than either TBI or PTSD alone. Thus treatment for those with comorbid TBI/PTSD may need to be adapted to use slower verbal processing, and also, because of this, clinicians need to carefully consider whether processing speed slowness may be contributing to clinical observations and test scores that suggest executive deficits, especially in veterans with comorbid TBI and PTSD. Some also suggest that persisting TBI cognitive symptoms might increase the risk for later development of PTSD. Likewise, depressed TBI patients have greater deficits in attention, memory and executive functioning than non-depressed

TBI patients. One study found that comorbid depression and TBI increased the incidence of impaired executive function by 30%. The polytrauma from blast TBI makes these patients especially vulnerable to psychopathology, and they require special care in special facilities with multidisciplinary teams of healthcare providers.

When considering options for treatment of, and/or rehabilitative interventions for, executive dysfunction, it appears that only the dopamine agonist medication and some complementary medicine approaches, like acupressure, have some efficacy for the specific medical treatment of executive dysfunction. Consequently, the most effective interventions for executive dysfunction are techniques that fall under the general heading of 'cognitive therapy'. Cognitive therapy relies on the ability of the patient to be able to 'think about thinking', i.e., metacognition, and creating new thinking patterns in a patient is the basis of cognitive rehabilitation. This is a practical application of cognitive therapy concepts originally identified with the work of Aaron Beck in the 1960s, and cognitive behavioral therapy (CBT) that has been shown to be efficacious for a number of psychological conditions, such as PTSD and other anxiety disorders. While the root cause of executive dysfunction in TBI is secondary to a physical injury of the brain, cognitive rehabilitation therapy approaches disorders with the concept that patients can overcome their deficits by developing new, more functional, ways of thinking.

One specific approach, the Metacognitive Strategy Instruction (MSI), which emphasizes development of metacognitive skills such as problem solving and organization and metacognitive strategies, has been recommended as a practice standard. The general recommendations for treatment and rehabilitation are: 1) use a holistic approach with multidisciplinary teams in the subacute phase; 2) undertake trials of some

medications; 3) use specific rehabilitation approaches to attention retaining and retraining of executive function skills; and 4) train patients in the use of supportive devices (memory book or electronic devices).

Self-awareness is an important variable in the CRT approach, as the ability to recognize problems caused by damaged brain function is important for the necessary motivation of the patient for rehabilitation and safe and independent functioning. The challenge when using a metacognitive approach is that the patient's thinking process is abnormal, yet this is what one has to work with. Decreased metagognitive self-awareness is highly correlated with increased problems in some components of the executive system. This strongly suggests the importance of integrating an overall assessment of cognitive functions with a specific evaluation of self-awareness, and also to treat self-awareness within a structured rehabilitation program

When applied to the practical aspect of teaching TBI patients how to overcome cognitive deficits, therapists use a range of simple to more difficult tasks in the same way that physical therapists work with patients who have lost limbs. In fact there is a direct parallel with many of those with severe TBI and severe wounds. The goal is not to cure but to find ways to compensate for deficiencies, including using external devices, such as memory books or electronic personal organizers with time reminders, which act as 'cognitive prosthetics'. While some challenges to CRT come from the insurance industry, given the significant issue of personnel cost, from a practical viewpoint of needing to help wounded warriors regain lost cognitive functions as effectively and efficiently as possible, CRT is clearly the clinical treatment of choice, along with other

holistic and multidisciplinary approaches to the whole person. This is time consuming and personalized rehabilitation, not a 'cook book', one-size fits all approach.

In summary, this journey has allowed the consolidation of peer-reviewed published articles from a wide range of different disciplines to focus on what is known about combat TBI, mainly due to blast, and how this can affect the cognitive domain that is critical for allowing a returning warrior to be able to carry out tasks of daily living and to be functionally independent as much as possible when retuning to duty or transitioning to civilian life.

Conclusions & Clinical Implications

Two questions were asked at the beginning of this doctoral project: 1) does combat TBI affect executive functioning and, if so, 2) are these changes amenable to treatment so that executive functioning of combat TBI patients can be improved for daily living requirements and also help to make the treatment of comorbid conditions more effective? We are now in a position to attempt to answer these questions and to draw some conclusions that might be clinically useful.

The short answer to the first question is yes, but we are not yet sure if this is any different from the effect of TBI from non-blast incidents. In fact the one article identified with this question directly assessed whether there are differences in the cognitive outcomes of TBI caused by blast compared with TBI due to other causes. The study compared performance on some standard neuropsychological tests by 102 military patients with TBI (61 due to blast trauma, 41 to non blast trauma). A thorough statistical analysis was completed. "Overall the results do not provide any strong evidence that

blast is categorically different from other TBI mechanisms, at least with regard to cognitive sequelae on select measures" (Belanger, H.G., et al, 2009, p 1).

However, we do know a lot about how combat TBI (mostly blast) differs in its initial event from non-combat TBI, and how polytrauma plays an important role in the course of the condition. We know for example, that the main difference with blast TBI (or BINT) is the greater comorbidity with physical injuries that accompany it (whether mild, moderate, or severe), especially with injuries to the head and neck and the sensory organs of sight and hearing, balance and coordination, and we have data on the incidence and prevalence of amputations (sometimes quadruple) that represent more than enough trauma for anyone person to face in their future. We also know about the comorbidity of PTSD and depression as psychopathology with combat TBI, and that while 78-85% of troops returning from combat through normal rotations do not have TBI, over 50% of the approximately 15-22% with TBI are not receiving any form of mental health care. Of those who were evacuated from the theater due to injuries, 28% had TBI of some level, mostly moderate or severe, but only 3% had penetrating head wounds that present another major constellation of physical and mental issues.

A great deal of research has been carried out over the past few decades measuring the cognitive changes in TBI patients from falls and accidents, but the literature is quite limited for studies specifically assessing executive function changes due to blast TBI. We know that the effects of blast on the brain are quite different from the effects of falls, accidents, or other events that are based on mechanical trauma. The blast waves that attack the body not only create situations of typical TBI (being thrown into the air and then 'falling', or being blasted against a wall or floor) but the kinetic energy from the

blast also invades the torso so that pressure waves ripple up to the brain from inside the body, and likely cause significant neurological trauma of a very different nature from that due to mechanical external forces.

Regarding treating executive dysfunction, there is a strong body of evidence that cognitive rehabilitation therapy (CRT) is the most appropriate therapeutic approach in dealing with all TBI cognitive deficits, including executive function. The research also suggests that cognitive rehabilitation therapy should be started as soon as possible after any physical wounds have been addressed. In concept, this is no different from physical therapy interventions for physically wounded warriors. For the large majority that has mTBI, therapy should be instituted as soon as executive dysfunction and other cognitive deficits have been identified. CRT can be viewed just like any other rehabilitation approach; there is a deficit (a missing or damaged cognitive domain) that has to be rehabilitated as much as possible, and where it is impossible to bring the patient back to full functioning (like with a missing limb) then a prosthetic device can be utilized (again, comparable to a prosthetic limb). While the warrior with TBI may never be 'whole' again, just like his triple-amputee buddy, there is confidence that he or she can be rehabilitated to perform as well as possible when integrated back into their unit or civilian society. Warriors consider TBI a legitimate wound of combat; but there is still a stigma about being treated for comorbid psychopathology, such as PTSD and/or depression.

Looking back on this project from where it started, from a clinical perspective of dealing with severely wounded TBI patients at a major military hospital, the framework for understanding what these warriors are experiencing and what is possible in helping them gain back some of their young lives has been worth the time and effort needed for

this project. As far as the second question is concerned, there is no doubt that treating executive dysfunction in these warriors can help them significantly with daily living requirements and how to gain back some of the executive function that has been lost so that their personal live and family relationships can be more meaningful. And treating executive dysfunction also enhances the effectiveness of the treatment of other conditions, both physical and psychological. By treating executive dysfunction through careful rehabilitation, compliance with scheduled pain medications is improved, working through PTSD using cognitive behavioral therapy is enhanced, and simply being able to cook a meal, a major test of executive function, can be achieved. Further, cognitive rehabilitation therapy can also facilitate reintegration into civilian society, or even rejoining a military unit depending on the severity of the executive dysfunction.

Future Research

There appear to be too many tests used to assess executive function that may not have been well validated, or investigated for appropriate reliability. This makes comparing the results of different studies difficult, as each testing battery could be assessing the same function from different perspectives and reporting executive function problems in different ways. There is no standardization of the measurement, even in a laboratory setting. This makes comparing therapeutic approaches difficult to determine clinical efficacy. A multidisciplinary group of expert researchers and clinicians from military medicine needs to reach a consensus and select a battery of tests from those already available with good ecological validity, that can be administered efficiently with a specific focus on the needs of combat soldiers. This would allow clinical researchers to

be report on the same data, and Department of Defense funding could support those willing to use the selected test battery. Some of the newer tests (e.g., BRIEF-A and BADS) should be evaluated for this study, as they have been specifically developed to assess executive functioning in the most ecologically valid manner. Of particular relevance to the acute hospital setting is the DEX questionnaire of the BADS test, when administered by a clinician (not patient or caregiver as originally designed).

Also, treatment guidelines for executive dysfunction therapy need to be developed based on the research data and the specific needs of military medicine. This would allow a consistent level of care across all branches of the uniformed services and within the Veterans Administration Health Care System. Of particular relevance to military medicine is the need to establish ecologically valid outcome measures that address the real needs of both the military structure and the warrior. Having outcome measures that are not able to predict the executive functioning of the warrior in a combat situation are of no value when making command decisions, and this also does not help the warrior, whose first instincts is to want to return to his/her unit. Neither is served well if the outcome measures from any therapy do not provide a direct answer to a simple question: Is this soldier ready to return to his/her unit?

Further, the use of computer programs for cognitive therapy should be advanced using the latest technology (including 3D projection) as part of the rehabilitation program. These young warriors, only now ending or recently out of their teens, are actively involved with computer-based games, and there is evidence that teen online problem solving can improve executive function. This needs to be investigated and possibly expanded so that these young patients can receive treatment based on the latest

computer video technology. While virtual reality technology has not yet shown itself to be an effective or efficient way to rehabilitate military personnel, this is another area requiring good applied research.

Given that executive function may be still be evolving when many warriors are exposed to BINT in their late teens, with resulting executive dysfunction, a study of what combat blast does to the developmental aspects of executive function, as opposed to what it might do to those who are over a certain age, needs to be carried out. Does BINT permanently change executive function in those under 20, for example, so that no matter what cognitive rehabilitation is carried out there will always be a predictable developmental deficit that will never respond to therapy?

Also, a longitudinal study needs to be implemented to follow the warriors with executive dysfunction, so that population studies over time can report how this 'signature injury' has affected the day-to-day quality of life, and human productivity and dignity, over the life span of those who have been injured as the result of service to our country. The multi-year long-term follow-up study authorized by a directive of the Department of Defense to study warriors with TBI must include those with executive dysfunction. This directive establishes the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee, and a commitment to research the effects of blast injuries by industry, academia, DoD components, and other Federal Agencies (U.S. Department of Defense, 2006).

Concluding Comments

This study ends with a short discussion on warrior resiliency. This was not considered a factor in the literature review on combat TBI and executive functioning, but it does play an important role in how we treat our wounded warriors and what makes them a unique population of patients. There is a structured program in the military to prepare warriors for combat and then to prepare them to return home. These two environments and experiences are so different that unless training is provided on how to adapt to both situations, many soldiers would not fare well and the incidence of stress related conditions (especially PTSD) would be significantly higher. This is a major initiative of the military, especially the Army.

The Defense Center of Excellence for Psychological Health and Traumatic Brain Injury (DCoE) has a Resilience and Prevention Directorate that defines resilience as "a set of actions and attitudes that prepare individuals and groups for adapting to challenging situations, establishing a 'new norm' and realizing one's potential for growth" (Van Dillen, T.A., 2010, p.1). This program of developing resilience, or mental toughness, is part of the Army's larger "Comprehensive Soldier Fitness" program that aims to ensure soldiers are as mentally tough as they are physically tough. There are two aspects to this program: pre-deployment, to build soldier resiliency by developing self-confidence and mental toughness; and post-deployment, to help the soldier transition from combat to normal home life. 'Battlemind', the term used to describe this change in a soldier to prepare for war, was developed to create psychological resiliency so that the soldier will have the will and spirit to fight and win in combat. The program also applies

to leaders, reservists, and families. "Battlemind is a soldier's inner strength to face fear and adversity in combat with courage" (Castro, C.A., et al, 2006, p. 42-1).

The warriors from Iraq and Afghanistan who are now facing years of suffering due to their voluntary service to our country are certainly resilient. There is no other population of patients with their level of courage and drive to succeed no matter what challenges they face physically and mentally. They are unique. Whatever the outcomes of any government program of research, there are promises that must be made and kept to compensate these warriors for what they have given to protect us and our country: total respect, sincere appreciation for their service, and the highest quality medical and mental health care for the remainder of their lives.

REFERENCES

Arnsten, A.F.T. & Li, B-M (2005). Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. *Biological Psychiatry*, 57:1377-1384

Baddeley, A. (1996). Exploring the central executive. *The Quarterly Journal of Experimental Psychology,* 49A(1):5-28

Baddeley, A. (1998). The central executive: a concept and some misconceptions. *Journal of the International Neuropsychological Society*, 4:523-526.

Baddeley, A. (2000). The episodic buffer: a new component of working memory? *Trends in Cognitive Sciences*, 4(11):417-423.

Baddeley, A. (2003). Working memory and language: an overview. *Journal of Communication Disorders,* 36:189-208

Bagiella, E., Novack, T.A., Ansel, B., Diaz-Arrastia, R., Dikmen, S., Hart, T. & Temkin, N. (2010). Measuring outcome in traumatic brain injury treatment trials: recommendations from the traumatic brain injury clinical trials network. *Journal of Head Trauma Rehabilitation*, 25(5):375-382

Banich, M.T., (2009). The search for an integrated account. *Current Directions in Psychological Science,* 18(2):89-94.

Baños, J.H., Novack, T.A., Brunner, R., Renfroe, S., Lin, H. & Meythaler, J. (2010). Impact of early administration of sertraline on cognitive and behavioral recovery in the first year after moderate to severe traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 25(5):357-361.

Belanger, H.G., Kretzmer, T., Yoash-Gantz, R., Pickett, T. & Tupler, L. (2009). Cognitive sequelae of blast-related *versus* other mechanisms of brain trauma. *Journal of the International Neuropsychological Society*, 15:1-8.

Bennett, P., Ong, B. & Ponsford, J. (2005). Measuring executive dysfunction in an acute rehabilitation setting: using the dysexecutive questionnaire (DEX). *Journal of the International Neuropsychological Society*, 11:376-385.

Bivona, U., Ciurli, P., Barba, C., Onder, G., Azicuda, E., Silvestro, D., Mangano, R., Rigob, J. & Formisano, R. (2008). Executive function and metacognitive self-awareness after severe traumatic brain injury. *Journal of the International Neuropsychological Society*, 14:862-868.

BlueCross BlueShield (2008, May). *Cognitive rehabilitation for traumatic brain injury in adults*. Tec Assessment, 25, 3. Blue Cross and Blue Shield Association. Electronically retrieved, February 6, 2011, from http://www.bcbs.com/blueresources/tec/vols/23/23_03.pdf

Burgess, P.W., Alderman, N, Evans, J., Emslie, H. & Wilson, B.A. (1998). The ecological validity of tests of executive function. *Journal of the International Neuropsychological Society*, 4:547-558.

Burgess, P.W., Alderman, N., Forbes, C., Costello, A., Coates, L.M-A., Dawson, D.R., Anmderson, N.D., Gilbert, S.J., DuMontheil, I., & Channon, S. (2006). The case for the development and use of "ecologically valid" measures of executive function in experimental and clinical neuropsychology. *Journal of the International Neuropsychological Society*, 12:194-209.

Campbell, T.A., Nelson, L.A., Lumpkin, R., Yoash-Gantz, R.E., Pickett, T.C. & McCormick, C. (2009). Neuropsychological measures of processing speed and executive functioning in combat veterans with PTSD, TBI and comorbid TBI/PTSD. *Psychiatric Annals*, 39(8):796-803.

Casscells, S.W. (2007). *Traumatic brain injury: definition and reporting*. The Assistant Secretary of Defense-Health Affairs, The Pentagon, Washington, DC. Electronically retrieved December 19, 2010, from http://www.health.mil/libraries/HA_Policies_and_Guidelines/07-030.pdf

Castro, C.A., Hoge, & Cox, A. (2006). Battlemind training: building soldier resiliency. In *Human dimension in military operations: military leaders strategies for addressing stress and psychological support* (pp. 42-1 to 42-6). Meeting proceedings RTO-MP-HFM-134, Paper 42. Neuilly-sur-Seine, France: RTO.

Cernak, I., & Noble-Haeusslein, L.J. (2010). Traumatic brain injury: an overview of pathobiology with emphasis on military populations. *Journal of Cerebral Blood Flow & Metabolism*, 30:255-266.

Cernak, I. (2010). The importance of systemic response in the pathobiology of blast-induced neurotrauma, *Frontiers in Neurology*, 1(151):1-9. doi:10.3389/fneur.2010.00151

Cernich, A.N., Kurtz, S.M., Mordecai, K.L. & Ryan, P.B. (2010). Cognitive rehabilitation in traumatic brain injury. *Current Treatment Options in Neurology*, 12:412-423.

Chamberlain, E. (2003). Behavioral assessment of the dysexecutive syndrome (BADS). *Journal of Occupational Psychology, Employment and Disability*, 5(2):33-37

Chaytor, N., Schmitter-Edgecombe, M. & Burr, R. (2006). Improving the ecological validity of executive functioning assessment. *Archives of Clinical Neuropsychology*, 21:217-227.

Christensen, B.K., Colella, B., Inness, E., Hebert, D., Monette, G., Bayley, M., & Green, R. (2008). Recovery of cognitive function after traumatic brain injury: a multilevel modeling analysis of Canadian outcomes. *Archives of Physical Medicine and Rehabilitation, 89(supplement)*:S3-S15.

Collette, F. & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neuroscience and Behavioral Review*, 26:105-125.

Cicerone, K., Levin, H., Malec, J., Stuss, D. & Whyte, J. (2006). Cognitive rehabilitation interventions for executive function: moving from bench to bedside in patients with traumatic brain injury. *Journal of Cognitive Science*, 18(7):1212-1222

Dawodu, S. (2009). Traumatic Brain Injury (TBI) – Definition, Epidemiology, Pathophysiology. *eMedicine, Medscape.com*. Electronically retrieved December 16, 2010 from http://emedicine.medscape.com/article/326510-print

Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury & Defense and Veterans Brain Injury Center (2009). *Cognitive rehabilitation for mild traumatic brain injury*. Report of a consensus conference, April 2009, Washington, DC.

ECRI Institute (2011). *Cognitive rehabilitation therapy for traumatic brain injury: what we know and don't know about its efficacy*. Electronically retrieved February 10, 2011, from

https://www.ecri.org/Documents/TA/Cognitive_Rehabilitation_Therapy_ECRI_Institute_012111.pdf

Elder, G.A., Cristian, A., (2009). Blast-related mild traumatic brain injury: mechanisms of injury and impact on clinical care. *Mount Sinai Journal of Medicine*, 76:111-118

Fassbender, C., Murphy, K., Foxe, J., Wylie, G., Javitt, D.C., Robertson, I.H. & Garavan, H. (2004). A topography of executive functions revealed by functional magnetic resonance imaging. *Cognitive Brain Research*, 20(2):132-143.

Faul M., Xu L., Wald M.M., Coronado V. (2010). *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths, 2002-2006.* Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control.

French, L.M. (2010). Military traumatic brain injury: an examination of important differences. *Annals of the New York Academy of Sciences*, 1208:38-45

Gilbert, S.J., Burgess, P.W. (2008). Executive function. *Current Biology*, 18(3):110-114.

Gioia, G.A., Kenworthy, L. & Isquith, P.K. (2010). Executive function in the real world: BRIEF lessons from Mark Ylvisaker. *Journal of Head Trauma Rehabilitation*, 28(6):443-439.

Gunning-Dixon, F.M. & Raz, N. (2003). Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. Neuropsychologia, 41:1929-1941.

Guskiewicz, K.M., Marshall, S.W., Bailes, J., McCrea, M., Cantu, R.C., Randolph, C., & Jordan, B.D. (2005). Association between recurrent concussions and late-life cognitive impairment in retired football players. *Neurosurgery,* 57(4):719-726.

Guskiewicz, K.M., Marshall, S.W., Bailes, J., McCrea, M., Harding, Jr., H.P., Mathews, A., Mihalik, & Cantu, R.C. (2007). Recurrent concussion and risk of depression in retired football players. *Medicine and Science in Sports and Exercise,* 39(6):448-456.

Halbauer, J.D., Ashford, J.W., Zeitzer, J.M., Adamson, M.M., Lew, H.L. & Yesavage, J.A. (2009). Neuropsychiatric diagnosis and management of chronic sequelae of war-related mild to moderate traumatic brain injury. *Journal of Rehabilitation Research & Development*, 46(6):757-796.

Harlow, J.M., (1848). Passage of an iron rod through the head. *Boston Medical and Surgical Journal*, 39:389-393 (in Neyland, T.C., 1999, p. 281-283).

Hartikainen, K.M., Wäljas, M., Isoviita, T., Dastidar, P., Liimatainen, S., Solbakk, A, Ogawa, K.H., Soimakallio, S., Ylinen, A. & Öhman, J. (2010). Persistent symptoms in mild to moderate traumatic brain injury associated with executive dysfunction. *Journal of Clinical and Experimental Neuropsychology*, 32(7):767-774.

Heilbronner, R.L., Bush, S.S., Ravdin, L.D., Bart, J.T., Iverson, G.L., Ruff, R.M., Lovell, M.R., Barr, W.B., Echmendia, R.J., & Broshek, D.K. (2009). Neuropsychological consequences of boxing and recommendations to improve safety: a National Academy of Neuropsychology education paper. *Archives of Clinical Neuropsychology*, 24:11-19.

High, W.M., Briones-Galang, M., Clark, J.A., Gilkison, C., Mossberg, K.A., Zgaljardic, D.J., Masel, B.E. & Urban, R.J. (2010). Effect of growth hormone replacement therapy on cognition after traumatic brain injury. *Journal of Neurotrauma*, 27:1565-1575.

Hoge, C.W., Castro, C.A., Messer, S.C., McGurk, D., Cotting, D.I. & Koffman, R.L. (2204). Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *New England Journal of Medicine*, 351:13-22.

Hoge, C.W., McGurk, D., Thomas, J.L., Cox, A.L., Engel, C.C., & Castro, C.A. (2008). Mild traumatic brain injury in U.S. soldiers returning from Iraq. *New England Journal of Medicine*, 358:453-463.

Hoge, C.W., Goldberg, H.M., & Castro, C.A. (2009). Care of war veterans with mild traumatic brain injury – flawed perspectives. *New England Journal of Medicine,* 360:1588-1591

IOM (Institute of Medicine) (2009). *Gulf War and Health, Volume 7: Long-term Consequences of Traumatic Brain Injury*. Washington, DC: The National Academies Press.

Jaffee, M.S. & Meyer, K.S. (2009). A brief overview of traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) within the Department of Defense. *The Clinical Neuropsychologist*, 23:1291-1298.

Jones, E., Fear, N. & Wessely, S. (2007). Shell shock and mild traumatic brain injury: a historical review. *American Journal of Psychiatry*, 164(11):1641-1645.

Jorge, R.E., Robinson, R.G., Moser, D., Tateno, A., Crespo-Facorro, B. & Arndt, S. (2004). Major depression following traumatic brain injury. *Archives of General Psychiatry*, 61:42-50.

Kennedy, J.E., Cullen, M.A., Amador, R.R., Huey, J. & Leal, F.O. (2010). Symptoms in military service members after blast mTBI with and without associated injuries. *NeuroRehabilitation.* 26: 191-197

Kennedy, J.E., Leal, F.O., Lewis, J.D., Cullen, M.A. & Amador, R.R. (2010). Posttraumatic stress symptoms in OIF/OEF service members with blast-related and non-blast-related mild TBI. *NeuroRehabilitation*, 26:223-231.

Kennedy, M.R.T., Coelho, C., Turkstra, L., Ylvisaker, M., Sohlberg, M.M., Yorkston, K., Chiou, H.H. & Kan, P.F. (2008). Intervention for executive functions after traumatic brain injury: a systematic review, meta-analysis and clinical recommendations. *Neuropsychological Rehabilitation*, 18(3):257-299

Kim, J., Whyte, J., Hart, T., Vaccaro, M., Polansky, M., & Coslett, H. B. (2005). Executive function as a predictor of inattentive behavior after traumatic brain injury. *Journal of the International Neuropsychology Society*, 11, 435-445.

Lipsky, R.H., Sparling, M. B., Ryan, L. M., Xu, K., Salazar, A. M., Goldman, D., & Warden, D. L. (2005). Association of COMT Val158Met genotype with executive functioning following traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences*, 17:4, 465-471.

Lipton, M.L., Gulko, E., Zimmerman, M.E., Friedman, B.W., Kim, M., Gellella, E., Gold, T., Shiftesh, K., Ardekani, B.A. & Branch, C.A. (2009). Diffusion-tensor

imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology*, 252(3):816-824.

Loosemore, M., Knowles, C.H., & Whyte, G.P. (2007). Amateur boxing and risk of chronic traumatic brain injury: systematic review of observational studies. *British Medical Journal (BMJ)*, 335:809-812

Lyketsos, C.G., Rosenblatt, A. & Rabins, P. (2004). Forgotten frontal lobe syndrome or "executive dysfunction syndrome. *Psychosomatics*, 45(3):247-255.

Mashour, G.A., Walker, E.E. & Martuza, R.L. (2005). Psychosurgery: past, present, and future. *Brain Research Reviews*, 48:409-419

Matlin, M.W. (2009). *Cognition.* New York, NY, John Wiley

McAllister, T.W. & Stein, M.B. (2010). Effects of psychological and biomechanical trauma on brain and behavior. *Annals of the New York Academy of Sciences*, 1208:46-57.

McCarthy, M. (2009). The jousting accident that turned Henry VIII into a tyrant. *The Independent on Sunday*, UK. Retrieved elctronically on January 30, 2011, fromhttp://www.independent.co.uk/news/uk/this-britain/the-jousting-accident-that-turned-henry-viii-into-a-tyrant-1670421.html

McFadden, K.L., Healy, K.M., Dettman, M.L., Kaye, J.T., Ito, T.A. & Hernandez, T.D. (2011). Acupressure as a non-pharmacological intervention for traumatic brain injury (TBI). *Journal of Neurotrauma*, 28(1):21-34.

Miller, E.K. (2000). The prefrontal cortex and cognitive control. *Nature Reviews: Neuroscience*, 1: 59-65

Miller, T.C. & Zwerdling, D. (2011, February 7). Scientific review kicks off to weigh treatment for brain-injured soldiers. *ProPublica*. Electronically retreieved February 9, 2011 from http://www.propublica.org/article/scientific-review-kicks-off-to-weigh-treatment-for-brain-injured-soldiers

Miotto, E.C., Evans, J.J., Souza de Lucia, M.C. & Scaff, M. (2008). Rehabilitation of executive dysfunction: a controlled trial of attention and problem colving treatment group. *Neuropsychological Rehabilitation*, iFirst, 1-24.

Moxon, D. (2000) *Memory*. Heinemann, Oxford, UK. Electronically retrieved, July 31, 2010, from http://books.google.com/books?id=Xy90vrTuZNQC&pg=RA1-PA4&lpg=RA1-PA4&dq=ebbinghaus+and+james+on+memory&source=bl&ots=FvLcj1rB5T&sig=yzavPrnd-M7RhirMRn36gF4gSfU&hl=en&ei=TYRUTMDmKoL68AbDvYD_BA&sa=X&oi=book_result&ct=result&resnum=4&sqi=2&ved=0CB8Q6AEwAw#v=onepage&q=ebbinghaus%20and%20james%20on%20memory&f=false

Nelson, L.A., Yoash-Gantz, R.E., Pickett, T.C. & Campbell, T.A. (2009). Relationship between processing speed and executive functioning performance among OEF/OIF veterans: implications for postdeployment rehabilitation. *Journal of Head Trauma Rehabilitation*, 24(1):32-40.

Newman, L.M., Trivedi, M.A., Bendlin, B.B., Ries, M.L. & Johnson, S.C. (2007). The relationship between gray matter morphometry and neuropsychological performance in a large sample of cognitively healthy adults. *Brain Imaging*

Behavior. Electronically retrieved, December 12, 2010, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2558675/

Neyland, T.C. (1999). Frontal lobe function: Mr. Phineas Gage's famous injury. *Journal of Neuropsychiatry and Clinical Neuroscience*, 11(2):280-283.

Okie, S. (2005). Traumatic brain injury in the war zone. *New England Journal of Medicine*, 352:2043-2047

Ord, J.S., Greve, K.W., Bianchini, K.J. & Aguerrevere, L.E. (2010). Executive dysfunction in traumatic brain injury: the effects of injury severity and effort on the Wisconsin Card Sorting Test. *Journal of Clinical and Experimental Neuropsychology*, 32(2):132-140.

Owens, B.D., Kragh, J.F., Wenke, J.C., Macaitis, J., Wade, C.E. & Holcomb, J.B. (2008). Combat wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *Journal of Trauma Injury, Infection, and Critical Care*, 64(2):295-299.

Porter, M.D., (2003). A 9-year controlled prospective neuropsychological assessment of amateur boxing. *Clinical Journal of Sport Medicine*, 13(6):339-352.

Proctor, A. & Zhang, J. (2008). Performance of three racial/ethnic groups on two tests of executive function: clinical implications for traumatic brain injury (TBI). *NeuroRehabilitation*, 23:529-536.

Rabin, L.A., Batt, W.B. & Burton, L.A. (2005). Assessment practices of clinical neuropsychologists in the United States and Canada: a survey of INS, NAN, and APA Division 40 members. *Archives of Clinical Neuropsychology*, 20:33-65.

Rabin, L.A., Roth, R.M., Isquith, P.K., Wishart, H.A., Nutter-Upham, K.E., Pare, N., Flashman, L.A. & Saykin, A.J. (2006). Self- and informant reports of executive

function on the BRIEF-A in MCI and older adults with cognitive complaints. *Archives of Clinical Neuropsychology*, 21:721-732.

Rabin, L.A., Barr, W.B. & Burton, L.A. (2007a). Effects of patient occupation and education variables on the choice of neuropsychological assessment instruments. *Applied Neuropsychology*, 14(4):247-254.

Rabin, L.A., Burton, L.A. & Barr, W.B. (2007b). Utilization rates of ecologically oriented instruments among clinical neuropsychologists. *The Clinical Neuropsychologist*, 21:727-743.

Rapoport, M. J, McCullagh, S., Shammi, P., & Feinstein, A. (2005). Cognitive impairment associated with major depression following mild and moderate traumatic brain injury. *Journal of Neuropsychiatry and Clinical Neurosciences*, 17:1, 61-65

Raz, N., Rodrigue, K.M. & Acker, J.D. (2003). Hypertension and the brain: vulnerability of the prefrontal regions and executive functions. *Behavioral Neuroscience*, 117(6):1169-1180

Risling, M. (2010). Blast induced brain injuries – a grand challenge in TBI research. *Frontiers in Neurology*, 1(1):1-2. doi:10.3389/fneur.2010.00001.

Robbins, T.W. & Roberts, A.C. (2007). Differential regulation of fronto-executive function by monoamines and acetylcholine. *Cerebral Cortex*, 17:i151-i160.

Rohling, M.L., Beverly, B., Faust, M.E. & Demakis, G (2009). Effectiveness of cognitive rehabilitation following acquired brain injury: a meta-analytic re-examination of Cicerone et al.'s (2000, 2005) systematic reviews. *Neuropsychology*, 23(1):20-39.

Salazar, A.M., Warden, D.L., Schwab, K., Spewctor, J., Braverman, S., Walter, J., Cole, R., Rosner, M.M., Ecklund, J. & Ellenbogen, R.G. (2000). Cognitive rehabilitation for traumatic brain injury: a randomized trial. *Journal of the American Medical Association*, 283(23):3075-3081.

Sayer, N.A., Chiros, C.E., Sigford, B., Scott, S., Clothier, B., Pickett, T. & Lew, H.L. (2008). Characteristics and rehabilitation outcomes among patients with blast and other injuries sustained during the Global War on Terror. *Archives of Physical Medicine and Rehabilitation*, 89:163-170.

Scheibel, R.S., Newsome, M.R., Troyanskaya, M., Steinberg, J.L., Goldstein, F.C., Mao, H. & Levib, H.S. (2009). Effects of severity of traumatic brain injury and brain reserve on cognitive-control related brain activation. *Journal of Neurotrauma*, 26:1447-1461.

Schniederman, A.I., Braver, E.R. & Kang, H.K. (2008). Understanding sequelae of injury mechanisms and mild traumatic brain injury incurred during conflicts in Iraq and Afghanistan: persistent postconcussive symptoms and posttraumatic stress disorder. *American Journal of Epidemiology*, 167(12)1446-1452.

Schultz, D.P. & Schultz, S.E. (2008). *A history of modern psychology.* (9th ed.). Belmont, CA Thomson Wadsworth.

Schutz, L.E. & Wanlass, R.L. (2009). Interdisciplinary assessment strategies for capturing the elusive executive. *American Journal of Physical Medicine & Rehabilitation*, 88(5):419-422.

Selassie, A.W., Zaloshnja, E., Langlois, J.A.,Miller, T., Jones, P., & Steiner, C. (2008). Incidence of Long-term Disability Following Traumatic Brain Injury

Hospitalization, United States, 2003. *Journal of Head Trauma Rehabilitation: Focus on Clinical Research and Practice,* 23(2):123-131.

Serino, A., Ciaramelli, E., Di Santantonio, A., Malagu, S., Servadei, F., & Ladavas, E. (2006). Central executive system impairment in traumatic brain injury. *Brain Injury,* 20(1): 23-32.

Shallice, T. (1982). Specific impairments of planning. *Philosophical Transactions of the Royal Society of London,* 298:199-219.

Spikman, J.M. & van der Naalt, J. (2010). Indices of impaired self-awareness in traumatic brain injury patients with focal frontal lesions and executive deficits: implications for outcome measurement. *Journal of Neurotrauma,* 27:1195-1202.

Struchen, M.A., Clark, A.N., Sander, A.M., Mills, M.R., Evans, G. & Kurtz, D. (2008). Relation of executive functioning and social communication measures to functional outcomes following traumatic brain injury. *NeuroRehabilitation,* 23:185-198.

Taber, K.H., Warden, D.L., & Hurley, R.A. (2006). Blast-related traumatic brain injury: what is known? *Journal of Neuropsychiatry and Clinical Neuroscience,* 18(2): 141-145.

Tanielian, T. & Jaycox, L.H. (Editors) (2008). *Invisible wounds of war: psychological and cognitive injuries, their consequences, and services to assist recovery.* RAND Center for Military Health Policy, Santa Monica, CA.

Terrio, H., Brenner, L.A., Invins, B.J., Chao, J.M., Helmick, K., Schwab, K., Scally, K., Bretthauer, R., & Warden, D. (2009). Traumatic brain injury screening:

preliminary findings in a US Army brigade combat team. *Journal of Head Trauma Rehabilitation*, 24:14-23.

Thaut, M.H., Gardiner, J.C., Holmberg, D., Horwitz, J., Kent, L., Andrews, G., Donelan, B. & McIntosh, G.R. (2009). Neurological music therapy improves executive function and emotional adjustment in traumatic brain injury rehabilitation. *Annals of the New York Academy of Sciences*, 1169:406-416.

Tilghman, A. (2011, January 1). Military insurer denies coverage of new brain injury treatment. *USA Today*. Electronically retrieved February 9, 2011, from http://www.usatoday.com/news/military/2011-01-01-brain-injury-insurer_N.htm

Tsaousides, T. & Gordon, W.A. (2009). Cognitive rehabilitation following traumatic brain injury: assessment to treatment. *Mount Sinai Journal of Medicine*, 76:173-181.

UnitedHealthcare (2010, March 26). *Cognitive Rehabilitation*. United HealthCare Services, Inc. (Policy 2010T0144H). Electronically retrieved, February 6, 2011, from https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Medical%20Policies/Cognitive_Rehabilitation.pdf

Uomoto, J.M. & Williams, R.M. (2009). Post-acute polytrauma rehabilitation and integrated care of returning veterans: towards a holistic approach. *Rehabilitation Psychology*, 54(3):259-269.

U.S. Department of Defense (2006). Directive 6025.21E: *Medical research for prevention, mitigation, and treatment of blast injuries*. Electronically retrieved

February 10, 2011, from http://www.dtic.mil/whs/directives/corres/pdf/602521p.pdf

U.S. Department of Defense (2010). 2000-2010: TBI Categories (Penetrating/Severe/Moderate/Mild/Not Classifiable). *Health.Mil, Military Health System.* Electronically retrieved December 18, 2010, from http://www.health.mil/Research/TBI_Numbers.aspx

U.S. Department of Defense (2011). Casualty Report. Electronically retrieved January 12, 2011, from http://www.defense.gov/news/casualty.pdf

U.S. Department of Health and Human Services (2003). Glasgow Coma Scale, Centers for Disease Control and Prevention. Electronically retrieved January 25, 2011, from http://www.bt.cdc.gov/masscasualties/pdf/glasgow-coma-scale.pdf

Van Dillen, T.A. (2010). Resilience related to TBI in the military: an overview. *Brain Injury Professional*, 7(3): 1-12. Electronically retrieved, February 6, 2011, from http://www.brainline.org/content/2010/10/resilience-related-to-tbi-in-the-military-an-overview.html

Wade, S.L., Walz, N.C., Carey, J., Williams, K.M., Cass, J., Herren, L., Mark, E. & Yeates, K.O. (2010). A randomized trial of teen online problem solving for improving executive function deficits following pediatric traumatic brain injury. *Journal of Head Trauma Rehabilitation*, 25(6):409-415.

Warden, D. (2006) Military TBI during the Iraq and Afghanistan wars. *Journal of Head Trauma Rehabilitation,* 21(5):398-402.

Warden, D.L., Gordon, B., McAllister, T.W., Silver, J.M., Barth, J.T., Bruns, J.,Drake, A., Gentry. T., Jagoda, A., Katz, D.I., Kraus, J., Labbate, L.A., Ryan, L.M.,

Sparling, M.B., Walters, B., Whyte, J., Zapata, A. & Zitnay, G. (2006). Guidelines for pharmacologic treatment of neurobehavioral sequelae of traumatic brain injury. *Journal of Neurotrauma*, 23(10):1468-1501.

Wilson, B.A., Evans, J.J., Emslie, H., Alderman, N. & Burgess, P. (1998). The development of an ecologically valid test for assessing patients with dysexecutive syndrome. *Neuropsychological Rehabilitation*, 8(3):213-228.

Zhang, L., Abreau, B.C., Seale, G.S., Masel, B., Christiansen, C.H. & Ottenbacher, K.J. (2003). A virtual reality environment for evaluation of a daily living skill in brain injury rehabilitation: reliability and validity. *Archives of Physical Medicine Rehabilitation*, 84:1118-1124.

Zelazo, P.D., Craik, F.I.M. & Booth, L. (2004). Executive function across the life span. *Acta Psychologica*, 115(2-3):167-183.

Zelazo, P.D. (2005). Executive function. *AboutKidsHealth*. Electronically retrieved November 30, 2010, from http://aboutkidshealth.ca/News/Executive-Function-Part-Six-Training-executive-function.aspx?articleID=8177&categoryID=news-type